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THE WESTERN Journal of Medicine

VOLUME 126 • NUMBER 1 **JANUARY 1977**

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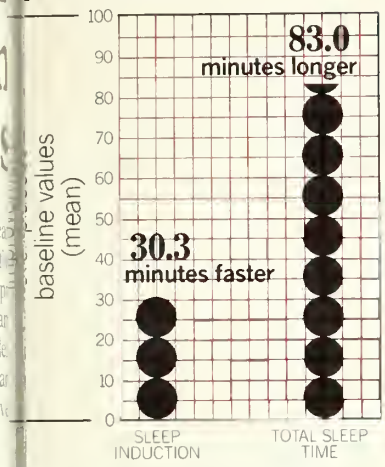

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REFERENCES:
1. Frost JD Jr: Data on file, Medical Department, Hoffmann-La Roche Inc., Nutley NJ
2. Data on file, Medical Department, Hoffmann-La Roche Inc., Nutley NJ
3. Robinson DS, Amidon EL: Interaction of benzodiazepines with warfarin in man, in *The Benzodiazepines*, edited by Garattini S, Mussini E, Randall LO. New York, Raven Press, 1973, p. 641

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References:
1. Dornfeld L, Kane R: Metolazone in essential hypertension: The long-term clinical efficacy of a new diuretic. *Curr Ther Res* **18**: 527-533, 1975.
2. Data on file, Medical Department, Pennwalt Prescription Products.

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(Continued on Page 10)

INTERNIST—MEDICAL DIRECTOR

Internist sought for full time academic position to serve as Medical Director of home care program and consultant in comprehensive medical clinic within the division of ambulatory and community medicine UCSF. Applicants should have experience in undergraduate teaching and interest in the management of chronic illness in ambulatory and homebound patients. Applicants must be certified in internal medicine and licensed in the State of California.

This position is at the assistant professor level and is available 1 July 1977. UCSF is an Equal Opportunity/Affirmative Action employer. Women and minorities are encouraged to apply. Address inquiries with C.V. to:

John J. Deller, MD, Chairman of Search Committee, Division of Ambulatory and Community Medicine, University of California, San Francisco A-405, before 31 January 1977.

PLASTIC SURGEON

Very nice Southeastern city now in need of a plastic surgeon. The location is Columbus, Georgia. This is an excellent practice opportunity! For further information send C.V. to: **Paul J. Holley, General Care Corp., 6213 Charlotte Ave., Nashville, Tenn. 37209**

(Continued from Page 9)

PHYSICIANS WANTED

OPHTHALMOLOGIST—Surgeon to join eye group. Prefer general ophthalmologist with subspecialty (not retina or plastics). Central California University town. Qualified retirement plan, and other corporate benefits. Send résumé to Box 9495, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

ER PHYSICIANS, FAMILY PRACTITIONERS, AND PEDIATRICIANS needed for 50 Physician multi-specialty practice. Contact Max F. Kersbergen, Administrator, The Alaska Clinic, 2841 DeBarr Road, Anchorage, Alaska 99504.

YOUNG GENERAL INTERNIST; full-time for teaching in-patient and ambulatory care in Family Practice Residency Program. Northridge Hospital Family Practice Center, 18406 Roscoe Blvd., Northridge, CA 91325. (213) 885-1261.

INTERNIST AND GENERAL PRACTITIONER: small, well established medical group in San Fernando Valley needs help to service expanding practice. Potential for early partnership. New clinic building with room for expansion. Contact R. C. Hurn, Administrator: 9628 Van Nuys Blvd., Panorama City, CA 91402, telephone (213) 893-9761.

EXCELLENT OPPORTUNITY for qualified, ambitious Family Practitioner. Full or part-time associate needed for long established private practice in South Bay area of Los Angeles. Participate on percentage basis. Excellent climate, schools, recreation. (213) 373-7369, L. Valkenburg, Bus. Mgr.

BOARD CERTIFIED PHYSICIAN—To serve as Medical Director for hospital based prepaid health plan in San Francisco; attractive salary and fringe benefits; Calif. license required. Send C.V. to Mr. J. Sidas, French Hospital, P. O. Box 7883, S.F., CA 94119.

INTERNIST (U.S. Medical School Graduate, Board eligible or Certified) for primary care, with cardiology emphasis, to join young progressive innovative group (Cardiology-2, Endocrinology, Hematology-Oncology) in moderate size California community near central coast. Corporate benefits. Respond with Curriculum Vitae and photograph to Box #9502, Western Journal of Medicine, 731 Market St., S.F., CA 94103.

CARDIOLOGIST OR INTERNIST experienced in ECG interpretation for modern new preventive and rehabilitative medicine clinic with a medically supervised exercise facility in Denver, Colorado and Newport Beach, California. Will practice non-invasive cardiology to include: physical examinations, consultations, treadmill stress testing, cardiac rehabilitation class, supervision, and diet analysis. No in-patients, no crisis medicine, 5 days—no nghts or weekends. Salary to $45,000 or negotiable with a percentage of profits. Malpractice Insurance and company benefits provided. Write Box No. 9503, Western Journal of Medicine, 731 Market St., S.F., CA 94103.

POSITIONS AVAILABLE FOR INTERNISTS OR CARDIOLOGIST. Board certified or Board eligible preferred. Beginning salary from $32,000 to $39,600 per year, depending upon qualifications, plus automatic pay bonus of $5,000 to $10,000 per year. Complete malpractice insurance coverage provided. Liberal fringe benefits—life insurance, health insurance retirement, 30 days vacation plus 15 days sick leave each year. An unexcelled opportunity to engage in a challenging medical practice in a rural setting offering unlimited recreational opportunities — hunting, fishing, boating, snow and water skiing, plus fresh, clean air in abundance. Contact: Norman C. Jorgenson, M.D., Chief of Staff, or Frank W. Caldwell, Director, Veterans Administration Hospital, Miles City, Montana 59301; telephone (406) 232-3060. Nondiscrimination in employment.

ORTHOPEDIC SURGEON: Board eligible or certified. Small group practice. Excellent Southern California location. For further information, please call E. Quinn, (714) 838-4744.

FAMILY PHYSICIAN: Board eligible or certified. Excellent Southern California location. Small private medical group. For further information, please call E. Quinn, (714) 838-4744.

PHYSICIANS WANTED

GENERAL PRACTITIONER wanted, MD or DO, Chinese preferable. Medical Clinic in Sunset area of S.F. Inquire at (415) 664-2248. Dr. Carmody.

FAMILY PHYSICIAN to join group of progressive family practitioners utilizing the POMR, audits, and P.A.'s and F.N.P.'s. Seeking physician with similar interests. Opportunity to participate in teaching program of Department of Family Practice in local medical school. Salary and fringe benefits competitive. Located in Sacramento area—a delightful place to live and work. Contact Charles A. Branthaver, M.D., collect (916) 444-9160.

BOARD CERTIFIED/ELIGIBLE INTERNIST with sub-specialty chest disease, needed as associate in Southern California seaside community of 60,000. Practice consists of hospital respiratory therapy departments, pulmonary function laboratories, bronchoscopy, respiratory therapy school and private office. Salary negotiable. Contact: Robert F. Fortin, M.D., Inc., 3170 Loma Vista Road, Suite A, Ventura, California 93003. (805) 648-3146.

WANTED RADIOLOGIST, Rocky Mountain Region, Board Certified or Eligible, to join solo radiologist. Prefer recent graduate University Program. Reply to Box 9504, Western Journal of Medicine, 731 Market St., S.F., CA 94103.

FAMILY PRACTITIONER needed to replace retiring member of Six man Medical Corporation. Small metropolitan area. Very friendly with close proximity to big Cities and beaches. Local City College and 4 year College with all social amenities and sport. 4½ day week, prepaid malpractice, on call shared by all in group. Competitive salary 1st year—full corporate stock holdership after 1st year. Full Corporate benefits immediately. Write: B. R. Ericsson, MD, Manor Medical Group, Inc., 223 China Grade Loop, Bakersfield, CA 93308.

SITUATIONS WANTED

GENERAL SURGEON, 54 years of age, experienced in chest and peripheral vascular surgery, wishes to return to rural living. Pacific Coast States preferred. All replies considered and answered. Write Box 9492, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

ELECTROCARDIOGRAPHY BY CORRESPONDENCE. For industrial offices, clinics, institutions, practitioners. A non-computer service. Write Box No. 9506, Western Journal of Medicine, 731 Market St., S. F., CA 94103.

AVAILABLE Anesthetist San Francisco Area. Experienced all techniques. Anesthesia Services (415) 391-3339.

ADOLESCENT PHYSICIAN/BOARD CERTIFIED PEDIATRICIAN, 34 yrs. U. Wash. trained, 3 yrs. PEDS', 1 adolescent), 3 yrs. exp. med. director large comprehensive adolesc. clinic. Seeking opportunity with teaching potential. M. S. Smith, MD, 5112 48th N.E., Seattle, WA 98105.

EMERGENCY ROOM POSITION WANTED, medium or large hosp. in Rocky Mountain states, middle aged, ambitious. Experienced in trauma, orthopedics; university trained, diplomate—Natl. Boards. Box No. 9507, Western Journal of Medicine, 731 Market St., S.F., CA 94103.

INTERNIST, ABIM, AOA, insurance background. Seeks administrative position in San Francisco. Write Box No. 9505, Western Journal of Medicine, 731 Market St., S.F., CA 94103.

MEDICAL EQUIPMENT WANTED

USED X-RAY—200 to 300 ma, in good operating condition. Contact Jan Vilhauer, DVM 6610 Mother Lode Dr., Placerville, CA 95667; (916) 622-3943.

SUITES FOR LEASE

CENTRAL ORANGE COUNTY HIGH RISE: Adjacent to large community hospital, ultra modern professional suites available, multi-specialties. Contact John Sainsevain, developer, at (714) 835-6003, 801 N. Tustin Ave., Santa Ana, CA 92705.

VACATIONS/MEDICAL PROFESSIONALS
TAX DEDUCTIBLE VACATIONS FOR MEDICAL PROFESSIONALS

Over 500 listings of national/international meetings in the medical sciences for 1977. Send a $10 check or money order payable to **Professional Calendars, P.O. Box 40083, Washington, D.C. 20016.**

SEMINAR IN HAWAII

APRIL 1977 IN HAWAII—ADOLESCENCE SEMINAR. Designed for physicians who care for adolescence. Write W. Schiner, Workshop Coordinator, 1319 Punahou Street, Honolulu, HI 96826.

PRACTICES FOR SALE

INTERNAL MEDICINE practice for sale. Leaving for academic position in May 1977. Will introduce to patients. Price negotiable. Contact: J. Schneider, MD, 5011 Geary Blvd., San Francisco, CA 94118. Phone (415) 661-5184 after 6 p.m.

FOR SALE Solo F.P. Santa Ana, Ca 49 yrs. retiring Mar. 77 Insurance Class I, select clientele, Exp. back and Front assistant, avail, well furn. 6 rm. off. plus lab. Principle, age grp. 40-80 potential referrals for younger grp. Contact Dr. Leecing 2515 N. Main St. Santa Ana, CA (714) 542-8883.

OUTSTANDING SAN FRANCISCO LOCATION. Close to several hospitals. Reasonable price. Terms available. Must leave March 1, 1977. Contact: Taylor Robinson, MD, 3611 Sacramento St., San Francisco, CA 94118, (415) 921-0865.

OFFICES FOR LEASE OR RENT

FOR RENT: The newest and largest professional building in the South San Diego community of Imperial Beach, suites available can be customized to suit tenant. This is excellent opportunity for pediatrics, gynecology, dermatology, ophthalmology, general surgery, general practice, internal medicine and psychiatry. Photos and particulars available upon request from John E. Geis, DDS, 1340 Coronado Ave., Suite 201, Imperial Beach, CA 92032; office (714) 424-3931.

CALIFORNIA—Woodland. Custom designed suite for lease in new medical-dental building across street from hospital and major medical clinic. Contact: Woodland Dental Group, 1204 Cottonwood Street, Woodland, California 95695. Phone (916) 662-5485.

MEDICAL SUITE—651 sq. feet, corner in complex with 4 Internists, 2 GP's, Orthopedist, Clinical Laboratory, Dentist, Physical Therapist, Maintenance, all utilities excepting electricity furnished. I. N. Tucker, MD, 25 Evergreen, Mill Valley, CA 94941. Tele: (415) 388-3088.

THREE SUITES in beautiful new medical-dental building in rapidly growing Tuolumne County. Need for: otolaryngologist, ophthalmologist, oral surgeon, internist, ob-gyn. Present occupants: general surgeon, family physician, podiatrist, dentist, two pediatricans, and two radiologists. Contact Ken Kessel, 2135 Mono Way, Sonora, CA 95370: (209) 532-2996.

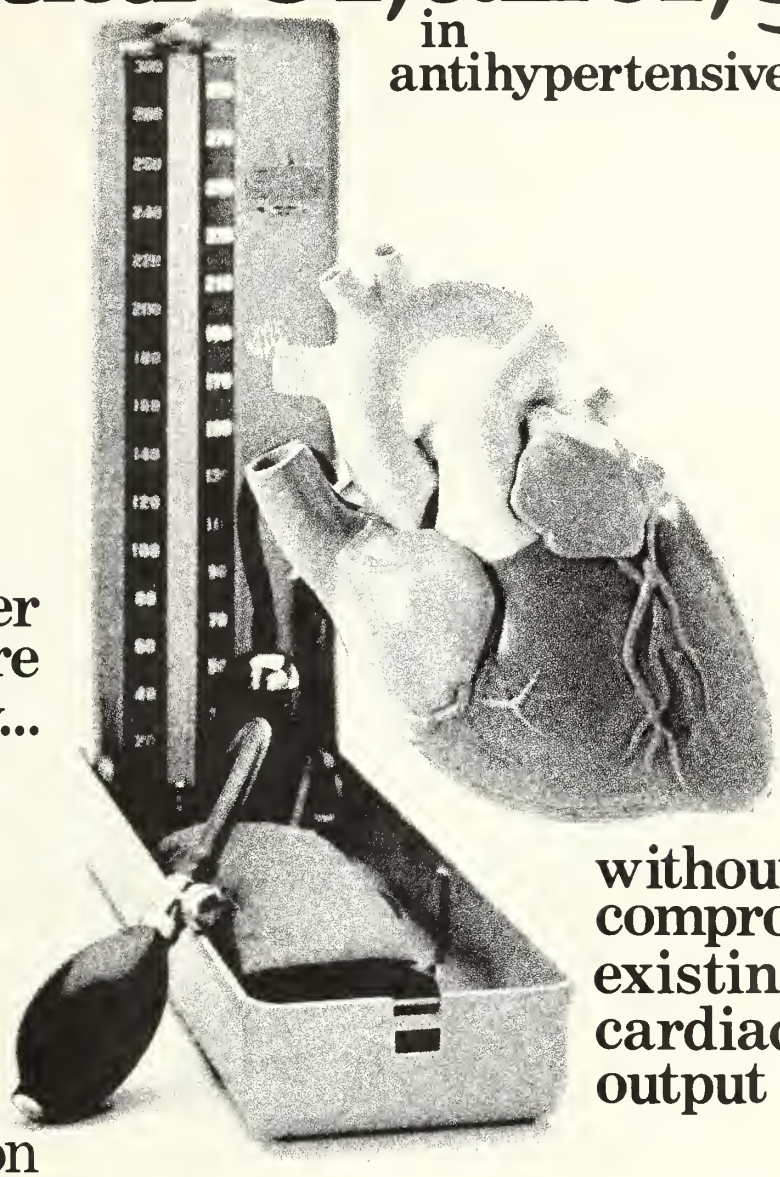
MODERN SUITE of medical offices consisting of private office, business office, three examination rooms, laboratory, private bath, and reception room, eleven hundred square feet, in Mt. Shasta, California, serving an area of 15,000 people. Fully equipped hospital (48 beds) less than one mile away, across the street from our future convalescent home. Ample parking space. Area is served now by two full time family physicians and one part-time family physician. Town is desperately in need of another physician. Contact D. L. Ratley, DDS, Inc., 611 South "A" St., Mt. Shasta, California 96067, Telephone (916) 926-4688. Mt. Shasta is a modern mountain community located in the center of skiing, fishing and hunting.

OFFICE SUBLET

DELUXE OFFICE SUITE—Fremont. Sublease Space or Time. Phone (415) 796-9454 Weekday mornings 9-12.

A Dual Challenge

in antihypertensive therapy



to lower blood pressure effectively...

without compromising existing cardiac output

in hypertension

TABLETS: 250 mg, 500 mg, and 125 mg

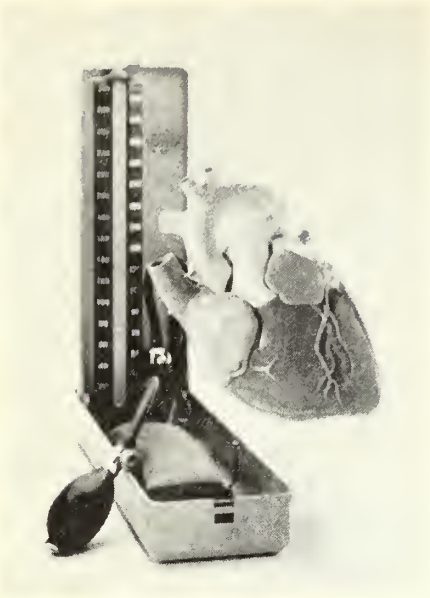
ALDOMET® (METHYLDOPA | MSD)

helps lower blood pressure effectively... usually with no direct effect on cardiac function–cardiac output is usually maintained

ALDOMET is contraindicated in active hepatic disease, hypersensitivity to the drug, and if previous methyldopa therapy has been associated with liver disorders.
It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed. For more details see the brief summary of prescribing information.

For a brief summary of prescribing information, please see following page.

MSD
MERCK SHARP & DOHME



in hypertension

ALDOMET®

(METHYLDOPA|MSD)

helps lower blood pressure effectively... usually with no direct effect on cardiac function– cardiac output is usually maintained

Contraindications: Active hepatic disease, such as acute hepatitis and active cirrhosis; if previous methyldopa therapy has been associated with liver disorders (see Warnings); hypersensitivity.

Warnings: It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed. Read this section carefully to understand these reactions.

With prolonged methyldopa therapy, 10% to 20% of patients develop a positive direct Coombs test, usually between 6 and 12 months of therapy. Lowest incidence is at daily dosage of 1 g or less. This on rare occasions may be associated with hemolytic anemia, which could lead to potentially fatal complications. One cannot predict which patients with a positive direct Coombs test may develop hemolytic anemia. Prior existence or development of a positive direct Coombs test is not in itself a contraindication to use of methyldopa. If a positive Coombs test develops during methyldopa therapy, determine whether hemolytic anemia exists and whether the positive Coombs test may be a problem. For example, in addition to a positive direct Coombs test there is less often a positive indirect Coombs test which may interfere with cross matching of blood.

At the start of methyldopa therapy, it is desirable to do a blood count (hematocrit, hemoglobin, or red cell count) for a baseline or to establish whether there is anemia. Periodic blood counts should be done during therapy to detect hemolytic anemia. It may be useful to do a direct Coombs test before therapy and at 6 and 12 months after the start of therapy. If Coombs-positive hemolytic anemia occurs, the cause may be methyldopa and the drug should be discontinued. Usually the anemia remits promptly. If not, corticosteroids may be given and other causes of anemia should be considered. If the hemolytic anemia is related to methyldopa, the drug should not be reinstituted. When methyldopa causes Coombs positivity alone or with hemolytic anemia, the red cell is usually coated with gamma globulin of the IgG (gamma G) class only. The positive Coombs test may not revert to normal until weeks to months after methyldopa is stopped.

Should the need for transfusion arise in a patient receiving methyldopa, both a direct and an indirect Coombs test should be performed on his blood. In the absence of hemolytic anemia, usually only the direct Coombs test will be positive. A positive direct Coombs test alone will not interfere with typing or cross matching. If the indirect Coombs test is also positive, problems may arise in the major cross match and the assistance of a hematologist or transfusion expert will be needed.

Fever has occurred within first 3 weeks of therapy, sometimes with eosinophilia or abnormalities in liver function tests, such as serum alkaline phosphatase, serum transaminases (SGOT, SGPT), bilirubin, cephalin cholesterol flocculation, prothrombin time, and bromsulphalein retention. Jaundice, with or without fever, may occur, with onset usually in the first 2 to 3 months of therapy. In some patients the findings are consistent with those of cholestasis. Rarely fatal hepatic necrosis has been reported. These hepatic changes may represent hypersensitivity reactions; periodic determination of hepatic function should be done particularly during the first 6 to 12 weeks of therapy or whenever an unexplained fever occurs. If fever and abnormalities in liver function tests or jaundice appear, stop therapy with methyldopa. If caused by methyldopa, the temperature and abnormalities in liver function characteristically have reverted to normal when the drug was discontinued. Methyldopa should not be reinstituted in such patients.

Rarely, a reversible reduction of the white blood cell count with primary effect on granulocytes has been seen. Reversible thrombocytopenia has occurred rarely. When used with other antihypertensive drugs, potentiation of antihypertensive effect may occur. Patients should be followed carefully to detect side reactions or unusual manifestations of drug idiosyncrasy.

Use in Pregnancy: Use of any drug in women who are or may become pregnant requires that anticipated benefits be weighed against possible risks; possibility of fetal injury can not be excluded.

Precautions: Should be used with caution in patients with history of previous liver disease or dysfunction (see Warnings). May interfere with measurement of: uric acid by the phosphotungstate method, creatinine by the alkaline picrate method, and SGOT by colorimetric methods. Since methyldopa causes fluorescence in urine samples at the same wavelengths as catecholamines, falsely high levels of urinary catecholamines may be reported. This will interfere with the diagnosis of pheochromocytoma. It is important to recognize this phenomenon before a patient with a possible pheochromocytoma is subjected to surgery. Methyldopa is not recommended for patients with pheochromocytoma. Urine exposed to air after voiding may darken because of breakdown of methyldopa or its metabolites.

Stop drug if involuntary choreoathetotic movements occur in patients with severe bilateral cerebrovascular disease. Patients may require reduced doses of anesthetics; hypotension occurring during anesthesia usually can be controlled with vasopressors. Hypertension has recurred after dialysis in patients on methyldopa because the drug is removed by this procedure.

Adverse Reactions: *Central nervous system:* Sedation, headache, asthenia or weakness, usually early and transient; dizziness, lightheadedness, symptoms of cerebrovascular insufficiency, paresthesias, parkinsonism, Bell's palsy, decreased mental acuity, involuntary choreoathetotic movements; psychic disturbances, including nightmares and reversible mild psychoses or depression.

Cardiovascular: Bradycardia, aggravation of angina pectoris. Orthostatic hypotension (decrease daily dosage). Edema (and weight gain) usually relieved by use of a diuretic. (Discontinue methyldopa if edema progresses or signs of heart failure appear.)

Gastrointestinal: Nausea, vomiting, distention, constipation, flatus, diarrhea, mild dryness of mouth, sore or "black" tongue, pancreatitis, sialadenitis.

Hepatic: Abnormal liver function tests, jaundice, liver disorders.

Hematologic: Positive Coombs test, hemolytic anemia. Leukopenia, granulocytopenia, thrombocytopenia.

Allergic: Drug-related fever, myocarditis.

Other: Nasal stuffiness, rise in BUN, breast enlargement, gynecomastia, lactation, impotence, decreased libido, dermatologic reactions including eczema and lichenoid eruptions, mild arthralgia, myalgia.

Note: Initial adult dosage should be limited to 500 mg daily when given with antihypertensives other than thiazides. Tolerance may occur, usually between second and third month of therapy; increased dosage or adding a thiazide frequently restores effective control. Patients with impaired renal function may respond to smaller doses. Syncope in older patients may be related to increased sensitivity and advanced arteriosclerotic vascular disease; this may be avoided by lower doses.

How Supplied: Tablets, containing 125 mg methyldopa each, in bottles of 100; Tablets, containing 250 mg methyldopa each, in single-unit packages of 100 and bottles of 100 and 1000; Tablets, containing 500 mg methyldopa each, in single-unit packages of 100 and bottles of 100.

For more detailed information, consult your MSD representative or see full prescribing information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, Pa. 19486 J6AM07(707)

MSD MERCK SHARP & DOHME

consider the effect on coexisting diabetes when you prescribe a vasodilator*

(POSTERIOR VIEW OF PANCREAS)

no interference in the management of the diabetic patient has been reported with

VASODILAN®
(ISOXSUPRINE HCl)

TABLETS, 20 mg.

the compatible vasodilator

Mead Johnson LABORATORIES

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***Indications:** Based on a review of this drug by the National Academy of Sciences-National Research Council and/or other information, the FDA has classified the indications as follows:

Possibly Effective:

1. For the relief of symptoms associated with cerebral vascular insufficiency.
2. In peripheral vascular disease of arteriosclerosis obliterans, thromboangiitis obliterans (Buerger's Disease) and Raynaud's disease.
3. Threatened abortion.

Final classification of the less-than-effective indications requires further investigation.

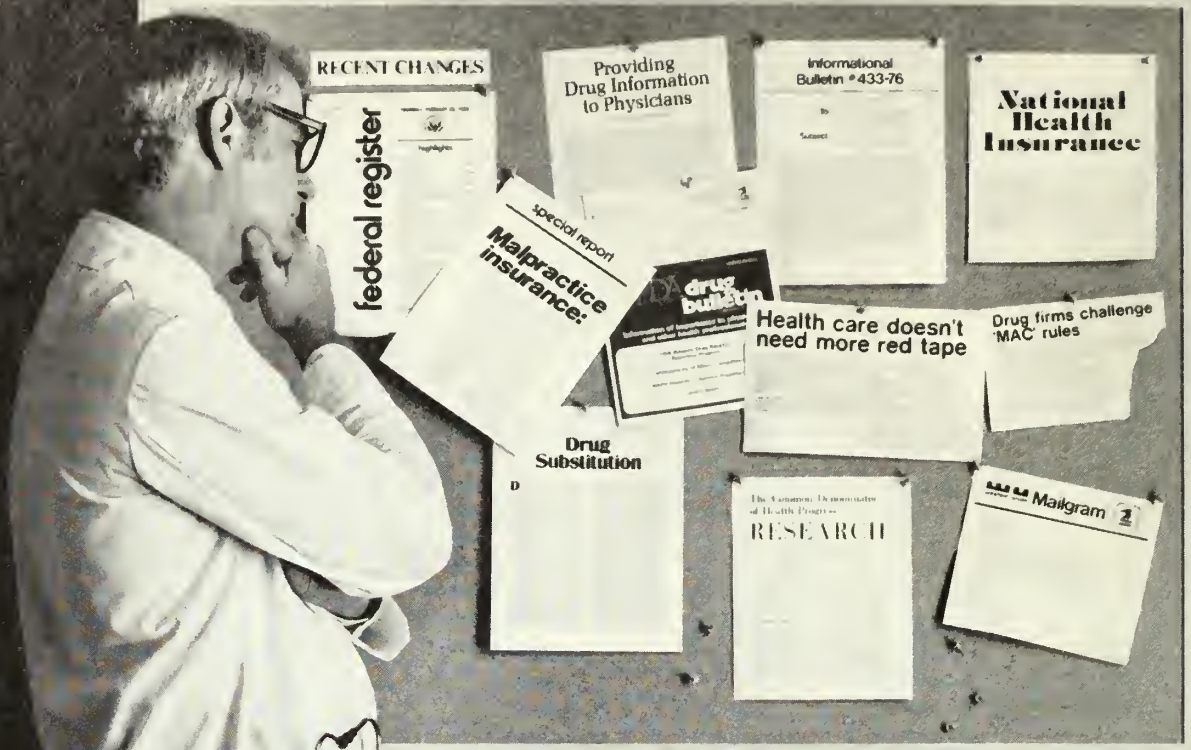
Composition: Vasodilan tablets, isoxsuprine HCl, 10 mg. and 20 mg.

Dosage and Administration: 10 to 20 mg. three or four times daily.

Contraindications and Cautions: There are no known contraindications to oral use when administered in recommended doses. Should not be given immediately postpartum or in the presence of arterial bleeding.

Adverse Reactions: On rare occasions, oral administration of the drug has been associated in time with the occurrence of severe rash. When rash appears, the drug should be discontinued. Occasional overdosage effects such as transient palpitation or dizziness are usually controlled by reducing the dose.

Supplied: Tablets, 10 mg.—bottles of 100, 1000, 5000 and Unit Dose; 20 mg.—bottles of 100, 500, 1000, 5000 and Unit Dose.


RECENT CHANGES
federal register
Providing Drug Information to Physicians
Informational Bulletin #433-76
National Health Insurance
special report
Malpractice insurance:
drug bulletin
Health care doesn't need more red tape
Drug firms challenge 'MAC' rules
Drug Substitution
RESEARCH
Mailgram

THERE ARE A LOT OF PEOPLE GETTING BETWEEN YOU AND YOUR PATIENT.

Medicine today is in the spotlight, subjected to all kinds of scrutiny. Your control over patient therapy is being monitored, judged and occasionally abrogated, sometimes by unknown third parties.

The worry is that in the wake of this focus, the relationship between you and your patient will be weakened, without offsetting benefits. Consider three examples:

Drug substitution In most states, pharmacy laws, regulations or professional custom stipulate that your non-generic prescriptions be filled with the precise products you prescribe. But in the last five years, a dozen or more State laws have been changed, permitting the pharmacist in most cases to select a product of the same generic drug to fill any prescription.

Ironically, this dilution of physician control has taken place against a background of growing evidence that purportedly equivalent drug products may be inequivalent, since neither present drug standards nor their enforcement are optimal. In fact, the FDA itself says it has not enforced the same standards for hundreds of "follow-on" products that it had applied to the original NDA approvals. Thus physician control over patient therapy is being eroded with a risk that patients may be exposed to drugs of uncertain quality.

The major advertised claim for substitution is reduced prescription prices for consumers. Yet no documentation of any significant savings has been produced.

MAC Maximum Allowable Cost, MAC for short, is a Federal regulation designed to cut the Government's drug bill by setting price ceilings for drugs dispensed to Medicare and Medicaid patients. Unless the prescriber certifies on the prescription that a particular product is medically necessary, the Government intends to pay only for the cost of the lowest-priced, purportedly-equivalent, generally-available product. The effect of the program may be that elderly and indigent patients will be restricted to products which someone in Washington believes are priced right. Practicing doctors will have little to say about administration of the program, since Government will have absolute authority to make its choices stick.

The drug lag The future of drug and device research depends upon a scientific and regulatory environment that encourages therapeutic innovations. The American pharmaceutical industry annually is spending more than $1 billion of its own funds and evaluating more than 1,200 investigational compounds in clinical research. Disease targets include cancer, atherosclerosis, viruses and central nervous system disorders, among others. But there is a major barrier to the flow of new drugs to your patients: The cost of the research is more than ten times what it was, per product, in 1962; and whereas governmental clearance of new drug applications took six months then, it commonly consumes two years now.

The FDA needs adequate time, of course, to consider data. But it is equally clear that the present approval process contributes to needless delay of needed therapy. That's why the increased efficiency of the drug approval process is vital to all our futures.

If these issues concern you, we suggest that you make your voice heard—among your colleagues and your representatives in State legislatures and in Washington.

It could make a difference in your practice tomorrow.

P·M·A

Pharmaceutical Manufacturers Association
1155 Fifteenth Street, N.W., Washington, D.C. 20005

AND

Western Scientific Assembly

March 4-9, 1977 • Disneyland Hotel • Anaheim

Registration opens Friday, March 4 at 7:30 a.m. in the Disneyland Hotel Convention Center Foyer

APPLICATION FOR HOTEL ACCOMMODATIONS

Your reservation request should include the definite date and hour of your arrival and departure.

All suite reservations must be cleared through the CMA Convention Office, San Francisco. If you are requesting a suite, direct your requests to: CMA Convention Office, 731 Market Street, San Francisco 94103.

Cancellations: Please notify Disneyland Hotel Reservations Department of all cancellations.

Changes: All other changes are to be made directly with the hotel at all times.

1977 ANNUAL SESSION • CALIFORNIA MEDICAL ASSOCIATION

Please circle desired accommodations:

DISNEYLAND HOTEL

	Garden	Towers
Single	$30.00	$38.00
Twin or Double	34.00	42.00
Triple or Quad	40.00	48.00
Suites: Sitting Room with 1 Bedroom		90.00
Sitting Room with 2 Bedrooms		125.00

Plus 6% city tax

Parking for registered guests is $1.00 for 24 hours.

If the rate you have requested is no longer available, the next available room category will be confirmed.

Please enclose first night's rent as deposit. Deposit can only be refunded if hotel is notified 5 days before arrival date.

Reservations will not be guaranteed if deposit is not received by February 2, 1977.

Send to: Disneyland Hotel Reservations
1150 West Cerritos Avenue
Anaheim, California 92803

Rate Requested _____

Arrival (date) _____ Hour _____ a.m. p.m. Departure (date) _____ Hour _____ a.m. p.m.

The name and address of each hotel guest must be listed. Include names and addresses of each person in a double or twin-bedded room, and names and addresses of **all other persons** for whom you are requesting reservations.

Your Name _____

Address _____

City and State _____ Zip Code _____

ADDITIONAL OCCUPANTS:

_____

In vitro susceptibility updated and still virtually unchanged

Schering

A five-year history of pathogen susceptibility to Garamycin® (gentamicin sulfate)—1971-1975

	1971	1972	1973	1974	1975
Gram-Negative Susceptibility No. of Patient Isolates	98% 89,317	97% 113,473	97% 127,763	97% 150,094	97% 193,626
Escherichia coli	99%	99%	99%	99%	99%
Proteus species, indole-negative	98%	99%	99%	99%	99%
Proteus species, indole-positive	97%	96%	94%	94%	92%
Pseudomonas aeruginosa	96%	96%	95%	94%	95%
Klebsiella-Enterobacter-Serratia	99%	98%	99%	99%	98%
Staphylococcal Susceptibility No. of Patient Isolates	97% 6,995	98% 11,109	98% 12,225	99% 18,352	99% 28,130
Staphylococcus aureus	97%	98%	98%	99%	99%
Staphylococcus epidermidis	97%	97%	98%	98%	98%

Source: PMR Bacteriologic Reports—1971-1975
These *in vitro* data are based on results obtained from a nationwide panel of 180 acute-care hospitals of 100 beds or more. All hospitals in the audit used the Kirby-Bauer method of disc sensitivity. Data are presented in unweighted form.

***In vitro* susceptibility data are not necessarily indicative of clinical effectiveness.**

See Clinical Considerations section which follows...

Garamycin® I.M./I.V.
gentamicin sulfate injectable
80mg/2ml.
40 mg/ml. Each ml. contains gentamicin sulfate equivalent to 40 mg. of gentamicin

The seven major gram-negative pathogens and *Staphylococci* remain highly susceptible...

Schering

Of the seven major gram-negative pathogens encountered in the hospital, 97 per cent remained sensitive to Garamycin *in vitro* over a five-year period; 99 per cent of *Staphylococci* remained sensitive.

GARAMYCIN® Injectable, brand of gentamicin sulfate, U.S.P., injection, 40 mg. per ml.
Each ml. contains gentamicin sulfate, U.S.P. equivalent to 40 mg. gentamicin
For Parenteral Administration

WARNING

Patients treated with GARAMYCIN Injectable should be under close clinical observation because of the potential toxicity associated with the use of this drug.

Ototoxicity, both vestibular and auditory, can occur in patients, primarily those with pre-existing renal damage, treated with GARAMYCIN Injectable usually for longer periods or with higher doses than recommended.

GARAMYCIN Injectable is potentially nephrotoxic, and this should be kept in mind when it is used in patients with pre-existing renal impairment.

Monitoring of renal and eighth nerve function is recommended during therapy of patients with known impairment of renal function. This testing is also recommended in patients with normal renal function at onset of therapy who develop evidence of nitrogen retention (increasing BUN, NPN, creatinine or oliguria). Evidence of ototoxicity requires dosage adjustments or discontinuance of the drug.

In event of overdose or toxic reactions, peritoneal dialysis or hemodialysis will aid in removal of gentamicin from the blood.

Serum concentrations should be monitored when feasible and prolonged concentrations above 12 mcg./ml. should be avoided.

Concurrent use of other neurotoxic and/or nephrotoxic drugs, particularly streptomycin, neomycin, kanamycin, cephaloridine, viomycin, polymyxin B, and polymyxin E (colistin), should be avoided.

The concurrent use of gentamicin with potent diuretics should be avoided, since certain diuretics by themselves may cause ototoxicity. In addition, when administered intravenously, diuretics may cause a rise in gentamicin serum level and potentiate neurotoxicity.

USAGE IN PREGNANCY Safety for use in pregnancy has not been established.

INDICATIONS GARAMYCIN Injectable is indicated, with due regard for relative toxicity of antibiotics, in the treatment of serious infections caused by susceptible strains of the following microorganisms.

Pseudomonas aeruginosa, Proteus species (indole-positive and indole-negative), *Escherichia coli* and *Klebsiella-Enterobacter-Serratia* species.

Clinical studies have shown GARAMYCIN Injectable to be effective in septicemia and serious infections of the central nervous system (meningitis), urinary tract, respiratory tract, gastrointestinal tract, skin and soft tissue (including burns).

Bacteriologic tests to determine the causative organisms and their susceptibility to gentamicin should be performed.

Bacterial resistance to gentamicin develops slowly in stepwise fashion; there have been no one-step mutations to high resistance.

In suspected or documented gram-negative sepsis, GARAMYCIN may be considered as initial therapy. The decision to continue therapy with this drug should be based on the results of susceptibility tests, the severity of the infection, and the important additional concepts contained in the Warning Box.

For suspected sepsis when the infecting organism is unknown, gentamicin may be administered in conjunction with a penicillin-type drug. Following identification of the organism and its susceptibility, appropriate antibiotic therapy should then be continued. In the neonate with suspected sepsis or staphylococcal pneumonia, a penicillin-type drug is also usually indicated as concomitant therapy with gentamicin.

GARAMYCIN Injectable has been shown to be effective in serious staphylococcal infections. It may be considered in those infections when penicillins or other less potentially toxic drugs are contraindicated and bacterial susceptibility testing and clinical judgment indicate its use.

CONTRAINDICATIONS A history of hypersensitivity to gentamicin is a contraindication to its use.

WARNINGS See Warning Box.

PRECAUTIONS Neuromuscular blockade and respiratory paralysis have been reported in the cat receiving high doses (40 mg./kg.) of gentamicin. The possibility of these phenomena occurring in man should be considered if gentamicin is administered to patients receiving neuromuscular blocking agents, such as succinylcholine and tubocurarine.

Treatment with gentamicin may result in overgrowth of nonsusceptible organisms. If this occurs, appropriate therapy is indicated.

ADVERSE REACTIONS:

Nephrotoxicity: Adverse renal effects, as demonstrated by rising BUN, NPN, serum creatinine and oliguria, have been reported. They occur more frequently in patients with a history of renal impairment treated with larger than recommended dosage.

Neurotoxicity: Adverse effects on both vestibular and auditory branches of the eighth nerve have been reported in patients on high dosage and/or prolonged therapy. Symptoms include dizziness, vertigo, tinnitus, roaring in the ears and hearing loss.

Numbness, skin tingling, muscle twitching, and convulsions have also been reported.

Note: The risk of toxic reactions is low in patients with normal renal function who do not receive GARAMYCIN Injectable at higher doses or for longer periods of time than recommended.

Other reported adverse reactions, possibly related to gentamicin, include increased serum transaminase (SGOT, SGPT), increased serum bilirubin, transient hepatomegaly, decreased serum calcium; splenomegaly, anemia, increased and decreased reticulocyte counts, granulocytopenia, agranulocytosis, thrombocytopenia, purpura, fever, rash, itching, urticaria, generalized burning, joint pain, laryngeal edema, nausea, vomiting, headache, increased salivation, lethargy and decreased appetite, weight loss, pulmonary fibrosis, hypotension and hypertension.

DOSAGE AND ADMINISTRATION

GARAMYCIN Injectable may be given intramuscularly or intravenously.

For Intramuscular Administration:

Patients with normal renal function

Adults: The recommended dosage for GARAMYCIN Injectable for patients with serious infections and normal renal function is 3 mg./kg./day, administered in three equal doses every 8 hours.

For patients weighing over 60 kg. (132 lb.), the usual dosage is 80 mg. (2 ml.) three times daily. For patients weighing 60 kg. (132 lb.) or less, the usual dosage is 60 mg. (1.5 ml.) three times daily.

In patients with life-threatening infections, dosages up to 5 mg./kg./day may be administered in three or four equal doses. This dosage should be reduced to 3 mg./kg./day as soon as clinically indicated.

In children and infants, the newborn, and patients with impaired renal function, dosage must be adjusted in accordance with instructions set forth in the Package Insert.

For Intravenous Administration:

The intravenous administration of GARAMYCIN Injectable is recommended in those circumstances when the intramuscular route is not feasible (e.g., patients in shock, with hematologic disorders, with severe burns, or with reduced muscle mass).

For intravenous administration in adults, a single dose of GARAMYCIN Injectable may be diluted in 100 or 200 ml. of sterile normal saline or in a sterile solution of dextrose 5% in water; in infants and children, the volume of diluent should be less. The concentration of gentamicin in solution in both instances should normally not exceed 1 mg./ml. (0.1%). The solution is infused over a period of one to two hours.

The recommended dose for intravenous administration is identical to that recommended for intramuscular use.

GARAMYCIN Injectable should not be physically premixed with other drugs, but should be administered separately in accordance with the recommended route of administration and dosage schedule.

HOW SUPPLIED GARAMYCIN Injectable, 40 mg. per ml., is supplied in 2 ml. (80 mg.) multiple-dose vials and in 1.5 ml. (60 mg.) and 2 ml. (80 mg.) disposable syringes for parenteral administration.

Also available: GARAMYCIN Pediatric Injectable, 10 mg. per ml., supplied in 2 ml. (20 mg.) multiple-dose vials for parenteral administration.

011 JUNE 1975
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For more complete prescribing details, consult Package Insert or Physicians' Desk Reference. Schering literature is also available from your Schering Representative or Professional Services Department, Schering Corporation, Kenilworth, New Jersey 07033.

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Refer to: Dempsey LC, Winestock DP, Hoff JT: Stab wounds of the brain. West J Med 126:1-4, Jan 1977

THE WESTERN
Journal of Medicine

Stab Wounds of the Brain

LAWRENCE C. DEMPSEY, MD; DAVID P. WINESTOCK, MD, *and* JULIAN T. HOFF, MD
San Francisco

Unlike the penetrating injuries to the brain caused by missiles, injuries by stabbing are largely restricted to the wound tract. Early recognition, debridement and judicious antibiotic therapy can limit or prevent complications in the management of stab wounds. Among the common sequelae of stab wounds of the brain are pneumocephalus, meningitis, intracerebral hemorrhage and direct blood vessel or nerve injury.

LOW-VELOCITY PENETRATING WOUNDS of the brain are uncommon because the skull usually provides an effective protective barrier. The skull can be penetrated easily, however, through its foramina and in areas of thin bone. Dujovny recently emphasized the vulnerability of the brain to penetrating wounds of the orbit and the thin calvarium of children[1] and Dolling and coworkers pointed out the relative ease with which the squamous portion of the temporal bone can be perforated in a child.[2] The adult calvarium is less easily traversed, yet stab wounds and their complications continue to be clinical problems. The case reports to follow exemplify not only the penetrability of the adult calvarium, but also early and delayed sequelae resulting from stab wounds of the brain.

Reports of Cases

CASE 1. A 43-year-old man lost consciousness minutes after having been stabbed with a screwdriver in the right temporal area. The 7 mm puncture wound extruded hematoma but not cerebral tissue. On neurological examination the patient was comatose and responded to pain with decerebrate posturing. Conjugate deviation of gaze to the left could not be overcome with the doll's eye maneuver. There were bilateral iridectomy residua, intact corneal reflexes, absent gag reflex and a flaccid left hemiplegia. An arteriogram showed right temporal lobe swelling but no abnormalities in the posterior fossa. Debridement by temporal craniectomy showed a narrow hemorrhagic tract with a few superficial bone fragments. Postoperatively the complete right gaze palsy resolved to a "one and a half" syndrome.[3] On an arteriogram done 16 days after injury a traumatic aneurysm was noted which had developed from the right superior cerebellar artery (Figure 1). The patient regained full alertness and comprehension over two weeks but had residual right pontine deficits including: left hemiplegia, right trochlear palsy, right internuclear ophthalmoplegia, ocular bobbing, palatal and pharyngeal myoclonus, and aphonia.

CASE 2. A 22-year-old man was admitted to hospital in an obtunded state after having been found in his bed in vomitus. Body temperature was 103.2°F (39.6°C), blood pressure was 150/90 mm of mercury and his neck was rigid; he responded to pain with nonpurposeful thrashing movements. Respirations were Cheyne-Stokes type. Fundi were normal, pupils were 4 mm in diameter and briskly reactive to light. Conjugate

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Dr. Hoff is the recipient of Teacher-Investigator Award NS11051.

Submitted April 14, 1976.

Reprint requests to: Editorial Office, Department of Neurological Surgery, University of California School of Medicine, San Francisco, CA 94143.

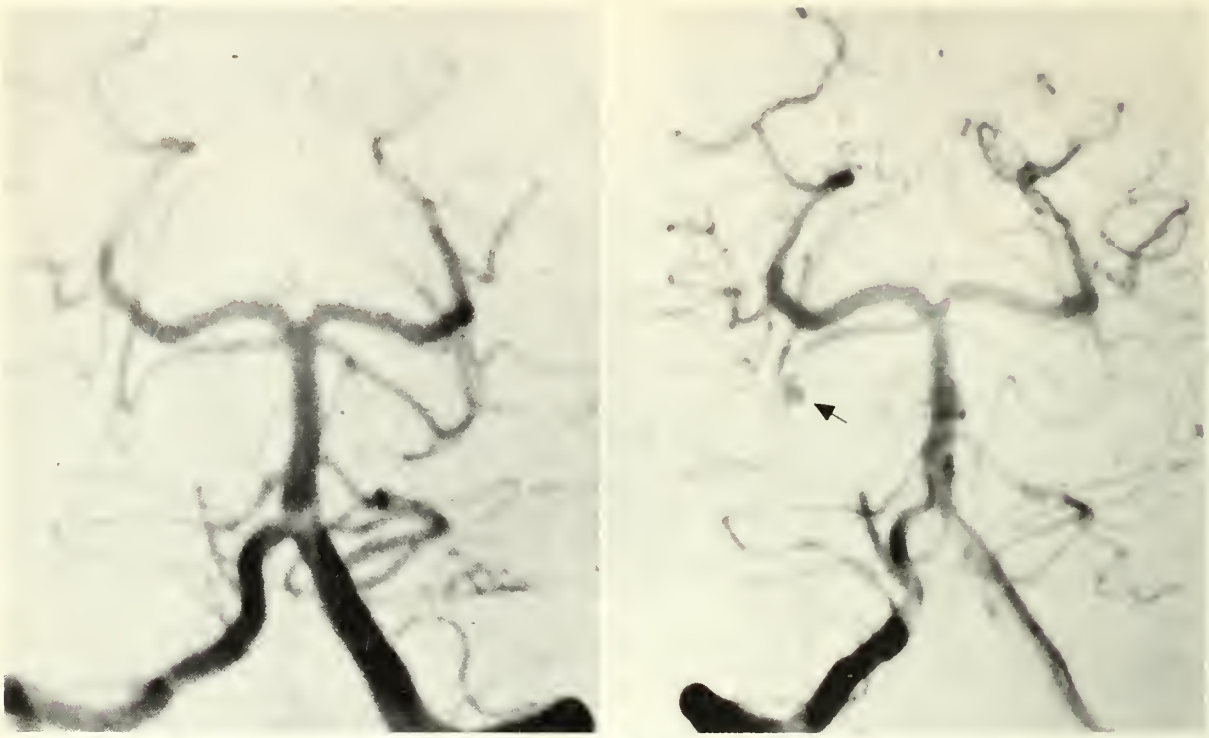

Figure 1.—Left, right vertebral angiogram on the day of injury. No abnormality is identified. **Right,** right vertebral angiogram 16 days after injury. An aneurysm of the right superior cerebellar artery is present **(arrow).**

deviation of gaze to the right was present, but could be overcome by doll's eye maneuver. Reflexes were 4+ throughout with bilateral Babinski signs. A lumbar puncture yielded bloody fluid with an opening pressure of 500 mm of water.

The patient became apneic during an arteriogram. The angiographs disclosed a very large posterior temporal mass (Figure 2). Angiographic signs of ventricular enlargement were present. A previously unrecognized 5 mm puncture wound was discovered 5 cm above and behind the meatus during head preparation for craniotomy. The large hematoma was evacuated. Tiny fragments of bone and hair were removed from the lacerated cortex and white matter. Postoperatively Cheyne-Stokes respirations returned, but the patient became apneic and died 24 hours later.

On autopsy an intraventricular clot and extensive hemorrhagic laceration of brain were noted.

Case 3. A 27-year-old schizophrenic man entered the hospital after stabbing a paring knife with a 4-inch blade into his forehead. Findings on examination were normal except for delusional ideation, and a 3 cm by 2 mm horizontal gash in the midline just above the nasion. Body temperature was normal. X-ray films of the skull showed a fracture through the right frontal sinus and pneumocephalus (Figure 3). Antibiotic therapy was begun. The wound was debrided and the dura closed. The patient remained afebrile until the sixth postoperative day when his temperature rose to 101.8°F (38.8°C) and he became incoherent. Findings on lumbar puncture showed Enterobacter meningitis which was eliminated by adding chloramphenicol to the antibiotic regimen. The patient recovered completely.

Case 4. A 22-year-old man was admitted to San Francisco General Hospital after having been assaulted. On physical examination an irregular 3 cm laceration in the superior posterior frontal area was found. Results of neurological examination were normal except for obtundation with preserved purposeful movements and a mild right hemiparesis. On radiographs of the skull a 3 cm linear skull fracture beneath the laceration was seen. Within 30 minutes of admission the patient's left pupil dilated and reacted poorly to light. Burr holes showed there to be intracranial hypertension without an extracerebral hematoma. An arteriogram done immediately after trephination confirmed temporoparietal swelling without a localized parenchymal hematoma. Intracranial pressure was monitored after operation by a sub-

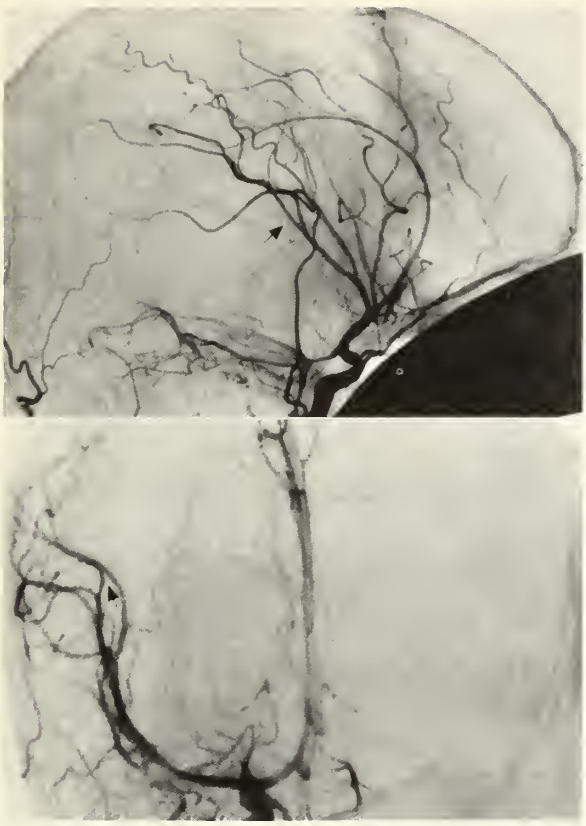

Figure 2.—Upper, right common carotid angiogram. Lateral projection. The posterior branches of the right middle cerebral artery are displaced anterosuperiorly **(arrow)** leaving a hypovascular area in the posterior temporal lobe. The anterior cerebral artery is straightened and elevated as a result of ventricular enlargement. **Lower,** right common carotid angiogram. Frontal projection. The sylvian point **(arrow)** is elevated. Ventriculomegaly is suggested by the increased distance between the anterior and middle cerebral arteries and the straightening of the anterior cerebral artery.

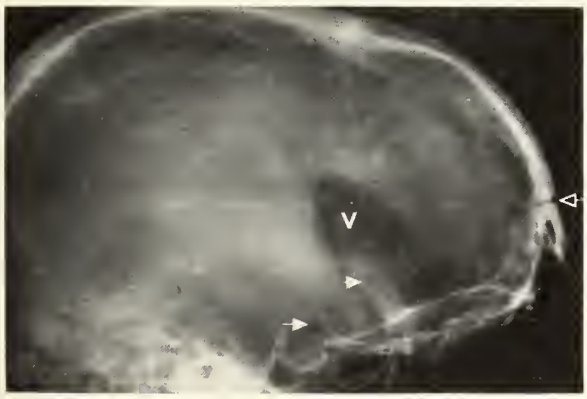

Figure 3.—Skull, lateral projection, brow up. There is a fracture through the frontal bone **(open arrow)** which involved the right frontal sinus. Air is present within the subarachnoid space **(closed arrows)** and the right ventricle **(V).**

dural catheter and managed with administration of mannitol and glycerol, and with controlled hyperventilation. A week later intracranial pressure rose to 50 mm of mercury, and both pupils became dilated and fixed. Increased serum osmolality prevented further therapy with osmotic agents. The patient became bradycardic and arrested while being ventilated.

On autopsy no infection was found but there was massive cerebral edema surrounding a deep laceration beneath the frontal fracture. Small bone fragments within brain tissue confirmed the penetrating nature of the injury.

Discussion

Medical reports of stab wounds of the brain date from as early as 1806.[4] Penfield[5] described the pathological features of experimental stab wounds with cannulas. Pilcher[6] compiled a lengthy list of objects known to have penetrated the brain that included knives, pitchforks, crochet hooks, knitting needles, breech pins, umbrella bibs, crowbars and iron rods. More recently, Markham[7] added car antennas to the list and Dolling added pairs of scissors.[2]

Nonmissile penetrating craniocerebral injuries are more amenable to treatment than are missile injuries. A stab wound creates a narrow hemorrhagic infarction which is largely restricted to the wound tract.[8] Concentric zones of coagulative necrosis do not result from stab wounds as they do from explosives and the cavitating forces of missiles.[8,9] Similarly contre coup injuries rarely occur, if at all, from stab wounds.[8] Unless the stabbing instrument is swept across the brain before withdrawal (as in case 4), the resultant lesion is focal. Therefore, in the absence of a direct injury to the brain stem or direct laceration of a major vessel, the prognosis for recovery may be good.

The reported stab wounds have usually penetrated the skull either in the vicinity of the orbits or in the temporal areas where the vault is thin.[2] Even full-thickness skull, however, will not stop a forcefully thrust sharp object. Although radiating fractures from the entry wound are common, the skull fracture often corresponds to the dimensions of the penetrating object.[8]

Early recognition of stab wounds of the brain is essential to ensure early treatment and a good outcome. Nonetheless, recognition remains difficult; neither the usual sites nor the appearances of entry wounds are characteristic of stab wounds

alone. Puncture wounds from screwdrivers and icepicks inside the hairline are especially easy to miss (case 2 provides an example). Congruent scalp lacerations and underlying fractures should always arouse suspicion.

Once recognized, treatment is straightforward, consisting of hemostasis, debridement and dural closure. The surgical approach is essentially that used for missiles[10]—debridement and dural repair.

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Diagnosing Acute Intussusception

The diagnosis of acute intussusception is suspected on the basis of age (80 percent of cases are in the first two years of life); sex (three boys to one girl); symptoms of intermittent colicky, severe, "labor" pains—even going into the knee-chest position; and appropriate signs of a palpable, sausage-shaped mass, frequently in the right upper quadrant under the liver where it is most difficult to feel. With family doctors taking particular note when a mother says something like "My child is having labor pains," we are picking up the diagnosis earlier. And, in 70 percent of these cases, a barium enema is effective and surgical operation is not required.

—TAGUE C. CHISHOLM, MD, *Minneapolis*

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Refer to: Sung JP, Grendahl JG, Levine HB: Intravenous and intrathecal miconazole therapy for systemic mycoses. West J Med 126:5-13, Jan 1977

Intravenous and Intrathecal Miconazole Therapy for Systemic Mycoses

JAMES P. SUNG, MD; JAN G. GRENDAHL, MA, *Fresno,* and H. B. LEVINE, PhD, *Oakland*

Ten patients with systemic mycoses, including five with fungal meningitis, were treated with intravenously or intrathecally administered miconazole, or both. Minimal inhibitory concentrations of miconazole for clinical isolates of Coccidioides immitis, Cryptococcus neoformans and Candida albicans were less than 0.6 μg per ml. Except for pruritis of variable degrees, the drug was well tolerated both intravenously and intrathecally by all patients. No measurable impairment of renal, hepatic or bone marrow function was observed in patients after 4½ months of intravenous therapy. No hematological or biochemical abnormalities and no evidence of recurrent coccidioidal osteomyelitis were observed in 16 months of follow-up in our first patient treated with this drug. Miconazole is apparently an effective antifungal drug of low toxicity and is a potentially useful agent for treatment of human systemic mycoses.

SYSTEMIC MYCOSES are increasingly encountered in various clinical situations.[1,2] Chemotherapy is restricted to only a few effective drugs; one of the most important, amphotericin B, is often nephrotoxic. There is clearly a need for an effective relatively nontoxic systemic antifungal agent.

Miconazole, a synthetic 1-phenethyl-imidazole derivative[3] (Figure 1), appears to be safe with broad-spectrum antifungal activity.[4,5] Studies by Swamy and co-workers,[6] and DeNollin and co-workers,[7,8] showed that miconazole altered the plasmalemma of Candida, producing impaired respiration and ultimately progressive cytoplasmic deterioration and cell lysis. At present, miconazole is experimentally used for the treatment of human systemic mycoses, including candidiasis, coccidioidomycosis, cryptococcosis, histoplasmosis and other pathogenic fungal infections.[9-14]

Ten patients were treated with intravenously given miconazole according to protocol approved by the Food and Drug Administration and the Subcommittee on Human Studies of Fresno Veterans Administration Hospital (FVAH). In addition, five of these patients also were given the drug intrathecally by special dispensation.

Materials and Methods

Since September 1974 ten male patients, 45 to 65 years old, with systemic fungal infections, were admitted to FVAH for treatment with miconazole after failure of other available antifungal therapy. Eight patients had disseminated cocci-

From the Department of Surgery and the Research Laboratory, Veterans Administration Hospital, Fresno, and the Naval Biological Research Laboratory, Naval Supply Center, Oakland.

Miconazole supplied by Janssen R & D, Inc., 501 George Street, New Brunswick, NJ 08901.

Submitted, revised, July 23, 1976.

Reprint requests to: James P. Sung, MD, Veterans Administration Hospital (113), 2615 East Clinton Avenue, Fresno, CA 93703.

ABBREVIATIONS USED IN TEXT

BUN = blood urea nitrogen
CBC = complete blood count
CSF = cerebrospinal fluid
CVC = central venous catheter
LDH = lactic dehydrogenase
SGOT = serum glutamic oxalic transaminase

dioidomycosis, four with coccidioidal meningitis. One patient had cryptococcal meningitis with multiple complications. One patient had a Candida infection and acute renal failure.

After obtaining an informed consent from each patient or his legal guardian, miconazole was administered according to the protocol. Renal, hepatic and hematological measurements and the central nervous system were evaluated before, during and after therapy.

Laboratory Studies

Before initiation of treatment. X-ray study of the chest, electrocardiogram, audiogram (whenever patient's condition would permit), blood volume measurement, complete blood count (CBC) and differential count, sedimentation rate, platelet count, coccidioidin skin test and serological test for patients wih coccidioidomycosis were done. Studies of other biochemical variables, including blood urea nitrogen (BUN), creatinine and creatinine clearance, cholesterol and triglycerides, serum glutamic oxalic transaminase (SGOT), lactic dehydrogenase (LDH), serum protein, alkaline phosphatase, bilirubin, electrolytes, serum iron and iron-binding capacity and fasting blood sugar, as well as analysis of urine and cerebrospinal fluid (CSF) examinations, were also done. Sputum examinations, bronchoscopy and bronchial wash for fungal and bacterial studies were done on patients with pulmonary lesions.

Weekly laboratory studies during therapy. CBC, sedimentation rate, platelet count, prothrombin time, electrolytes, BUN, creatinine, fasting blood sugar, alkaline phosphatase, bilirubin, SGOT and LDH studies and analysis of urine were done.

Follow-up studies. Most of the above-mentioned laboratory studies were also done immediately after completion of the therapy and repeated at one-to-two-month intervals after discharge.

Therapy

Intravenous Therapy. A central venous catheter (CVC) was placed either by the percutaneous subclavian route or via cephalic vein cutdown to

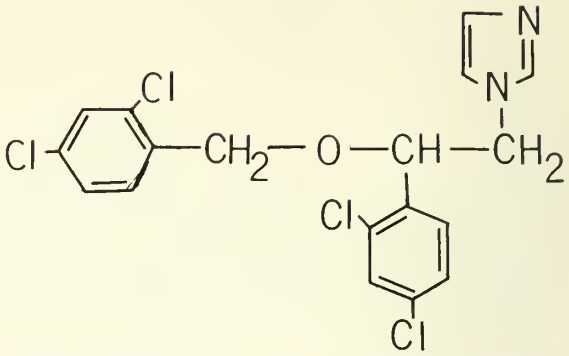

Figure 1.—Structural formula of miconazole nitrate.

avoid repeated venous punctures and prevalent thrombophlebitis of peripheral veins. Central venous catheters were kept open with 500 ml of an appropriate intravenous fluid per 24 hours. The catheter site was cleansed and dressed with betadine gauze every three days. Therapy was initiated with 200 mg of miconazole diluted with 50 to 100 ml of an intravenous fluid infused via a piggyback over a period of 15 to 30 minutes every eight hours. Each patient was monitored by electrocardiogram (ECG) during the first few infusions to assure there were no adverse cardiac effects. If no side effects developed after two days, the daily dosage was progressively increased to a maximum of 1,000 mg every eight hours. Serum and CSF concentrations of the drug were measured. At the termination of therapy, catheter tips were cultured for fungi and bacteria.

Intrathecal Therapy. A 22-gauge spinal needle was used to enter into the following interspaces: (a) lumbar region at the 3rd to 4th or 4th to 5th interspace; (b) cervical region between C1 and C2 interspace; (c) cisternal reservoir. A 26-gauge needle was used if a shunt or Ommaya reservoir was available. The maximum dosage of miconazole was 20 mg per injection via the lumbar route and 15 mg per injection via the C1 to C2 interspace, cisternal reservoir, Ommaya reservoir or shunt.

A three-syringe technique was used as follows. After positioning the spinal needle in the appropriate interspace, the first syringe was used to remove CSF for laboratory studies. A second syringe was connected and 8 to 10 ml of CSF removed. A third syringe containing miconazole was connected and an additional 6 to 8 ml of CSF withdrawn. This syringe was disconnected to allow complete mixing of the CSF-miconazole solution. After mixing, the syringe was reconnected and the miconazole-CSF mixture injected

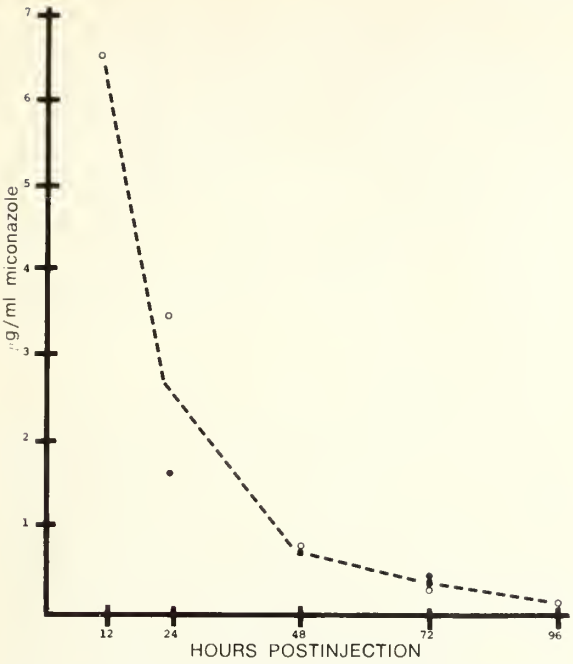

Figure 2.—Cisternal concentrations of miconazole following 20 mg lumbar injection in a coccidioidal meningitis patient.

over a 90 to 180 second period. Following this, the second syringe was reconnected and the CSF reinjected to flush the needle and immediate area.

The first injection was given by lumbar puncture. After injection the patient was placed in a Trendelenburg position for 90 to 180 minutes. Unlike recommendations for other drugs, miconazole was not administered in 10 percent glucose solution because its specific gravity is higher than the 10 percent glucose. Determinations of miconazole levels in CSF were made from cisternal fluid (Figure 2). Succeeding intrathecal injections were alternated between lumbar, cervical (C1-C2) and cisternal punctures every three to seven days. We found that alternating injection sites and flushing the spinal needle with pure CSF decreased the incidence and extent of chemical arachnoiditis, as occurred in Case 4.

In Vitro *Microbial Sensitivity to Miconazole*

Clinical isolates of fungi from these patients and species of opportunistic pathogens were tested for *in vitro* sensitivity to miconazole. Minimal inhibitory concentrations were determined by the agar dilution method[15] (Table 1). Miconazole was found to be inhibitory to Gram-positive bacteria as well as Coccidioides immitis, Aspergillus flavus, Cryptococcus neoformans and Candida albicans.

Results

Toxicity. No serious systemic toxicity resulted from intravenous or intrathecal miconazole treatment. Several minor side effects occurred in most of the patients, including nausea with or without vomiting, blurring of vision, dryness of eyes, arthralgia of the knees and, most commonly, pruritis of variable anatomical involvement. Pruritis was controlled by oral administration of diphenhydramine (Benadryl®). Other side effects subsided spontaneously when miconazole dosages were reduced below 600 mg per injection.

Hematology. Findings on studies of patients' hemoglobin and hematocrit values were variable. No change in serum iron and iron-binding capacity was noted. A frightening but apparently harmless phenomenon was observed in patients' peripheral blood smears. The plasma appeared to be saturated with oil, making it difficult to prepare smears. This peculiar phenomenon occurred in three patients when the infusion dose was greater than 600 mg every eight hours and given in more than 48 hours. The blood returned to normal spontaneously within 72 hours when the infusion dose was decreased to below 600 mg every eight hours. The possibility of the cumulative miconazole diluent, Cremophor EL (polyethoxylated castor oil), being the cause of this phenomenon should be considered. Coombs' tests (direct and indirect), as well as other laboratory examinations, gave findings within normal limits. Other investigators have observed rouleaux formation,[13] but none was noted here.

Cardiac-Respiratory. A total of 1,917 infusions have been carried out and 44 of these infusions were conducted with ECG monitor. No adverse effects on the cardiac-respiratory systems were observed when 800 mg of the drug was given in a period of five minutes or longer. Variable degrees of tachycardia and tachypnea were observed when the same dose was infused in less than two minutes. A ventricular tachycardia occurred during one infusion when 800 mg of the drug was given into the superior vena cava in less than one minute. The cardiac arrhythmia responded promptly when 50 mg of lidocaine was immediately administered intravenously. In the same patient, no further arrhythmia occurred when the same dosage was infused over a period of 15 minutes during subsequent injections.

Hepatic and Renal. In nine of the 10 patients, no measurable abnormal findings on liver func-

tion tests were observed. Only in Case 7 was an increase in preexisting jaundice noted. No evidence of increasing the concurrent renal disease was observed in one patient with chronic nephropathy. No adverse effects were found even when therapy was administered to one patient with acute renal failure.

Central Venous Catheter. We have had no problems of phlebitis because all of our infusions were given through a central venous catheter. The duration of the CVC placement in the superior vena cava varied from 14 to 156 days with an average of 61 days. All cultures taken from the tips of these catheters at the termination of treatment were negative for fungi or bacteria, even though only two patients received another antibiotic.

Pharmacokinetics. A maximum serum concentration[16] of the drug was found to be greater than 7.5, 7.5, 2.3 and 1.8 μg per ml 15 minutes after 1,000, 800, 600 and 400 mg of miconazole, respectively, were given intravenously. The disappearance of bioactive drug from serum involved an early rapid decay phase with a half-life of less than 60 minutes and a late, slow phase (Figure 3). Lewi and co-workers[17] have postulated a triphasic curve.

Miconazole does cross the blood-brain barrier to some extent. CSF concentrations of the drug one hour after an intravenous infusion of 800 mg were 0.1 μg per ml in four patients with coccidioidal meningitis and two patients without meningitis, and 0.3 μg per ml in one patient with cryptococcal meningitis. After intrathecal injection of 20 mg of miconazole via lumbar route in a patient with coccidioidal meningitis, 6.5, 2.4, 0.77 and 0.24 μg per ml of miconazole were found in the cerebrospinal fluid at the cisternal level at 12, 24, 48 and 72 hours, respectively (Figure 2). Bioactive concentrations of miconazole are higher and maintained longer in CSF after intrathecal administration than in serum after intravenous infusion (Figures 2 and 3).

Clinical Results. The clinical results of this experience are briefly described in the case reports.

Reports of Cases

CASE 1. The patient was a 50-year-old black man with severe disseminated coccidioidomycosis and whose clinical course was previously reported in this journal.[12] Hepatic, renal, hematological and biochemical variables have been checked monthly and no abnormalities in 16 months of follow-up have been observed. The complement fixation antibody titer decreased from 4+ at 1:256 dilution to 4+ at 1:32 dilution.

CASE 2. A 45-year-old white man had brittle diabetes with marginal nephropathy and recurrent pulmonary coccidioidomycosis of 25 years duration. Despite numerous courses of amphotericin-B therapy, a tensional pneumothorax developed from a ruptured coccidioidal cavity of the left lung in 1972 which required a resection of the cavity. Subsequently, a new lesion developed in the right lung which progressively enlarged. Sputum cultures yielded C. immitis. The fasting blood glucose level was 400 mg per 100 ml. An x-ray study of the chest showed a cavitary lesion measuring 5 by 6 cm in the right upper lung. After administration of 61 grams of miconazole in 60 days of treatment, it was seen on an

TABLE 1.—*Minimal Inhibitory Concentrations of Different Microbial Species to Miconazole*

Culture	*Number of Cultures Tested*	*μg of Miconazole/ml Agar*						*Control*
		20	10	5	2.5	1.2	0.6	
Escherichia coli	3	+	+	+	+	+	+	+
Flavobacterium	1	−	−	−	±	±	±	+
Proteus morgani	1	+	+	+	+	+	+	+
Proteus rettgeri	1	+	+	+	+	+	+	+
Pseudomonas aeruginosa	3	+	+	+	+	+	+	+
Serratia marcescens	1	+	+	+	+	+	+	+
Staphylococcus aureus	3	−	−	−	−	−	±	+
Staphylococcus epidermidis	2	−	−	−	−	−	±	+
Streptococcus pyogenes	1	−	−	−	−	−	−	+
Aspergillus flavus	7	−	−	−	±	+	+	+
Cryptococcus neoformans	1	−	−	−	−	−	−	+
Coccidioides immitis	7	−	−	−	−	−	−	+
Candida albicans	1	−	−	−	−	−	−	+

+ Indicates growth; no inhibition.
− Indicates no growth; complete inhibition.
± Cannot be determined.

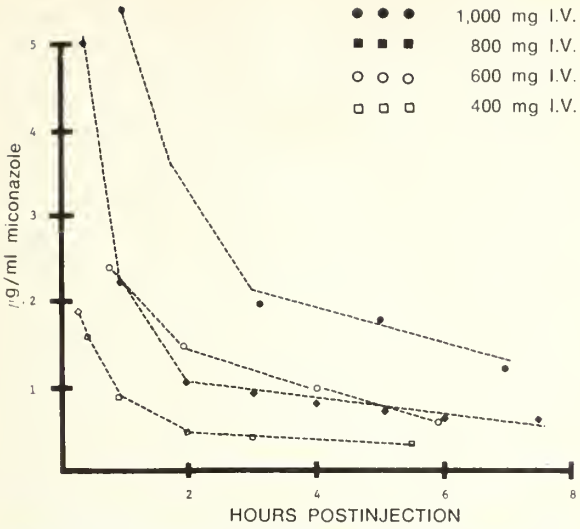

Figure 3.—Plasma concentrations of miconazole following intravenous injection.

x-ray study that the cavity had decreased in size, but the sputum cultures remained positive. No hematological or biochemical abnormalities were noted during 14 months of follow-up.

CASE 3. A 55-year-old Mexican-American man received amphotericin B since 1966 for disseminated coccidioidomycosis. In April 1970 C. immitis was cultured from a Baker's cyst removed from the left popliteal space. The patient was admitted to hospital on numerous occasions since 1970 for incision and drainage of coccidioidal abscesses of the left knee and intravenous and intraarticular amphotericin-B therapy. During the past two years the left knee was immobilized in a plaster cast but the coccidioidal synovitis progressed. On admission, the left knee measured 40.8 cm in diameter and the right knee was 33 cm. Several abscesses were noted in the posterior aspect of the left knee and cultures grew C. immitis. X-ray studies of the left knee showed no bone lesions. After eight weeks of intravenous therapy with miconazole, the abscesses had healed. The circumference of the left knee decreased from 40.8 to 35.5 cm and the patient gained full range of motion. There were no untoward effects and no recurrent disease in 13 months of follow-up.

CASE 4. The condition of a 65-year-old Mexican-American man was rapidly deteriorating during the final course of amphotericin B therapy for disseminated coccidioidomycosis. He refused further amphotericin treatment and was referred for a trial of miconazole. Levels of cerebrospinal fluid protein, glucose and cells were normal; complement fixation test was not done. After six weeks of miconazole treatment, some of the subcutaneous abscesses had healed. The patient gained weight and strength and experienced no untoward effects from the drug. During the three months of intravenous therapy with miconazole, coccidioidal meningitis developed. Studies of cerebrospinal fluid gave the following findings: protein, 780 mg per 100 ml; glucose, 28 mg per 100 ml; 138 cells with 48 percent polymorphonuclear, and complement fixation titer 4+ at 1:32 dilution. The patient became comatose. Treatment with intrathecal injections of miconazole was begun in addition to intravenous therapy. After five days of intrathecal injections, the level of consciousness improved. The patient became oriented by the tenth day following intrathecal treatment. However, arachnoiditis at the site of injection became a problem as evidenced by pain, induration and difficulty in entering into the subarachnoid spaces. The intrathecal method, as described earlier, was initiated and the problem of arachnoiditis was eliminated. After 26 intrathecal injections in 46 days, the CSF protein level decreased to 25 mg per 100 ml, glucose increased to 67 mg per 100 ml, complement fixation titer decreased to 4+ at 1:4 dilution and there were no cells. Despite a pronounced improvement in the meningitis, the disseminated disease progressed. The disease was complicated by congestive heart failure, pneumonitis, Gram-negative bacteremia and bacterial urinary tract infection. Despite vigorous medical management, the patient died 59 days after the intrathecal treatment. A total of 212 grams of miconazole had been given intravenously in 144 days and 420 mg of miconazole given intrathecally in 46 days. There was no change in the hematological or biochemical values. On autopsy, no evidence of meningitis was seen on either gross or microscopic examination. Cultures from the brain tissue and CSF were negative for C. immitis, but cultures from the subcutaneous abscesses, liver, kidneys and adrenal glands were positive.

CASE 5. A 50-year-old white man was admitted to Fresno Veterans Administration Hospital with a blood pressure of 60/30 mm of mercury, pulse 180 per minute, and hemoglobin value of 5 grams. A large artery blood loss from a preampullar ulcer embedded into the head of the pancreas was quickly controlled. Postoperatively, there developed shock-lung syndrome, acute pancreatitis with pancreatic ascites, acute renal failure

and a Candida infection in the abdominal wound and the site of CVP cutdown. Treatment was carried out with tracheostomy and positive end expiratory pressure (PEEP) to support the respiratory insufficiency. The acute pancreatitis and acute renal failure were treated by carefully monitoring fluids, electrolytes and acid-base balance, and peritoneal lavage with physiological saline. Although acute renal failure occurred and blood cultures were negative, 400 mg of miconazole was given intravenously every eight hours for the Candida infection. After seven days of treatment, cultures from the abdominal wound and CVP cutdown site were negative and administration of miconazole was discontinued. The patient had an uneventful recovery. There were no biochemical abnormalities noted in 11 months of follow-up.

CASE 6. A 55-year-old white man was treated with intravenous and intrathecal administration of amphotericin B for coccidioidal meningitis since February 1973. Unfortunately, the patient was extremely sensitive to amphotericin and a nearly fatal reaction to the first infusion occurred. Because of the extreme sensitivity to amphotericin, it required an average of 14 to 18 hours to infuse 20 mg of amphotericin per day for six days and 0.5 mg intrathecally on the seventh day. During the course of treatment, an obstructive hydrocephalus developed which required a right ventriculoatrial shunt. The patient was unable to leave his bed, was verbally unresponsive and required a feeding gastrostomy. Since 1974 he had received intermittent intrathecal suppression therapy with amphotericin. He was referred for a trial of miconazole therapy. On examination the patient, who was in a wheelchair, was found to be in a confused condition. He was able to obey simple commands but his answers were inappropriate. Findings on CSF examination showed a protein level of 88 mg per 100 ml, a glucose level of 49 mg per 100 ml and 13 lymphocytes. The CSF complement fixation titer on a test done six weeks before admission was 4+ at 1:16 dilution. Many leukocytes were noted on analysis of urine; results of other laboratory studies were within normal limits. At the end of five weeks of intrathecal and intravenous therapy, mental and physical improvement was seen. On CSF studies, a protein level of 40 mg per 100 ml, glucose value of 55 mg per 100 ml, no cells and a negative complement fixation titer were noted. Results of a CSF examination from a lumbar puncture done four months after discharge showed a protein level of 27 mg per 100 ml, glucose value of 64 mg per 100 ml, no cells and a negative complement fixation titer. The patient is doing well.

CASE 7. A 59-year-old white man was transferred to Fresno Veterans Administration Hospital with the diagnosis of cryptococcal meningitis, chronic liver disease, bone marrow depression due to antifungal drug toxicity, subacute bacterial endocarditis, left cerebral infarctions and chronic brain syndrome. This patient had received intravenously and intrathecally given amphotericin B and 5-fluorocytosine for six months for treatment of cryptococcal meningitis. In the final course of therapy more than 100 μg per ml of amphotericin was not inhibitory to the yeast *in vitro*. The patient's condition was deteriorating rapidly. On physical examination at admission, the patient was noted to be obtunded and responsive only to strong painful stimuli. Face, arms, buttocks and ankles were edematous with scattered ecchymoses, and a large decubitus ulcer was present in the right hip. The liver was enlarged and granular to palpation. The CSF protein level was 250 mg per 100 ml and glucose value was 5 mg per 100 ml. India ink preparation and cultures were positive for Cryptococcus. The organism was identified as Cryptococcus neoformans sensitive to less than 0.6 μg per ml of miconazole *in vitro*. The blood glucose value was 125 mg per 100 ml; hemoglobin, 7.8 gm per 100 ml; hematocrit reading, 19.9 percent; leukocyte count, 3,000; platelets less than 50,000; prothrombin time, 32 percent, total bilirubin, 3.6 mg per 100 ml; creatinine, 2.1 mg per 100 ml, and BUN 11 mg per 100 ml. Three days after intravenous and intrathecal therapy with miconazole, the level of consciousness improved. On the tenth day of treatment, the patient was more alert and able to eat and talk well, and the CSF protein value had decreased to 100 mg per 100 ml, glucose had increased to 33 mg per 100 ml and CSF cultures and India ink preparation were negative for Cryptococcus. On the evening of the same day, a fever up to 102°F developed. In the next three days jaundice increased. His condition rapidly worsened and the patient died on the 14th day of treatment. On autopsy multiple old and recent infarctions of the brain, severe cirrhosis of the liver, aplastic bone marrow and hypertensive cardiovascular disease were found. Cultures from the brain tissue and CSF were negatime for cryptococci yeast.

CASE 8. A 60-year-old black man had disseminated coccidioidomycosis with coccidioidal synovitis of the right knee and congestive heart failure from syphilitic aortitis since 1962. In 1963 surgical operation on the heart was carried out for aortic insufficiency. Numerous courses of amphotericin B treatment had been given. Since 1969, because of azotemia and proteinuria, treatment was confined to aspiration and intraarticular injections of amphotericin. The synovitis had progressively worsened. On examination a pronounced cardiomegaly was noted with a Grade IV systolic murmur heard over the entire chest. The right knee was swollen, tender and aspiration yielded 100 ml of thick pus yielding a positive culture for C. immitis. A coccidioidin skin test was negative. Analysis of urine showed 4+ protein; serum complement fixation titer was 4+ at 1:128 dilution. BUN was 32 mg per 100 ml; creatinine, 3.1 mg per 100 ml; hemoglobin, 10 gm per 100 ml. Intravenous treatment with miconazole was begun. During the four-month course of therapy congestive heart failure, pulmonary edema and a bacterial infection of the urinary tract—which was treated and improved—developed. Cultures from the right knee continue to yield C. immitis after four months of therapy and miconazole treatment is being continued. There have been no untoward effects and no evidence of worsening of the concurrent renal disease.

CASE 9. In a 64-year-old white man obstructive hydrocephalus from coccidioidal meningitis developed during intravenous and intrathecal treatment with amphotericin B. In October 1975 a ventriculoperitoneal shunt procedure was carried out. The shunt became infected and disfunctional and required revision. The patient was admitted to Fresno Veterans Administration Hospital one week after revision. On examination the patient, who was lying in bed with an indwelling Foley catheter, was noted to be obtunded. He was emaciated and verbally unresponsive. On CSF studies, the protein level was 300 mg per 100 ml, glucose value was 33 mg per 100 ml, there were 16 lymphocytes and a complement fixation titer of 4+ at 1:16 dilution. Staphylococcus epidermidis was cultured from the shunt reservoir. Hemoglobin was 7.5 grams per 100 ml; BUN, 11 mg per 100 ml; creatinine, 1.2 mg per 100 ml. Intravenous and intrathecal treatment with miconazole for coccidioidal meningitis was carried out, and also intravenous and intrareservoir administration of methicillin for sterilization of the reservoir *in situ,* as recommended by McLaurin.[18] Cultures for Staphylococcus epidermidis from the reservoir became negative after two weeks of treatment. After the patient was given 76.5 grams of miconazole intravenously in 86 days and 204 mg of miconazole intrathecally in 17 injections in 64 days, studies of CSF from the cisternal reservoir showed a protein level of 21 mg per 100 ml, glucose value of 88 mg per 100 ml, no cells and a negative complement fixation titer. CSF from a lumbar tap showed a protein value of 88 mg per 100 ml, glucose value of 76 mg per 100 ml, no cells and a complement fixation titer of 4+ at 1:2 dilution. Unfortunately, the clinical course was complicated by pulmonary tuberculosis, congestive heart failure, pneumonitis, Gram-negative bacteremia and urinary tract bacterial infections. The patient remains in a critical condition.

CASE 10. In a 49-year old white man headache and right third cranial nerve palsy developed during intravenous and intrathecal therapy with amphotericin B for coccidioidal meningitis. He was referred for miconazole treatment. On admission he was found to have a paralysis of the right third cranial nerve. In lumbar CSF, protein value was 288 mg per 100 ml, glucose level was 40 mg per 100 ml and there were 69 lymphocytes per cu mm. The CSF complement fixation titer had been 4+ at 1:16 dilution four weeks before admission. The patient was given 40 gm of miconazole intravenously and 160 mg intrathecally in 35 days of treatment. At the end of therapy, lumbar CSF protein value was 90 mg per 100 ml, glucose was 54 mg per 100 ml and there were 9 lymphocytes per cu mm. The CSF was negative by complement fixation test. The right third cranial nerve palsy had progressively improved. There were no untoward effects from the miconazole but there was a nearly fatal complication from an intracisternal hemorrhage due to trauma during the last cisternal injection. He was treated for this and recovered. The patient was discharged 2½ months after admission and is doing well.

Discussion

Use of intravenously given miconazole was initially studied in a moribund patient who was suffering from severe disseminated coccidioidomycosis after failure of other available chemotherapy.[12] A prompt clinical improvement oc-

curred in this patient and generated our interest in further evaluation of this drug. Clinical experience detailed in this report suggests the potential role of this agent in the treatment of human systemic mycoses.

More than 90 percent of miconazole is rapidly bound by the plasma protein after intravenous infusion.[17] Detectable concentrations of the drug in serum decline very rapidly (Figure 3). The question of what is the optimum therapeutic dosage and how frequently the drug should be administered has not been answered. Dosages of 400 to 600 mg infused through a central venous catheter every eight hours were tolerated well by average adults, even though most were in poor condition. We recommend routine use of a central venous catheter for prolonged intravenous administrations because this will obviate repeated venous punctures and problems of phlebitis of the peripheral veins.

Miconazole does cross the blood-brain barrier to some extent. Three patients with cryptococcal meningitis have been successfully treated with intravenously given miconazole alone by other investigators (personal communication with Dr. Weinstein of Peter Bent Brigham Hospital, Boston). However, in case of coccidioidal meningitis, intrathecal therapy has been necessary as shown in one of our patients (Case 4).

Since there was no information regarding the use of intrathecal miconazole, the patients we treated intrathecally were initially on empirical trial. The clinical and laboratory data we gained from these experiences have been invaluable.

Intrathecal administration of the antifungal drugs remains the mainstay of therapy in order to achieve a maximum drug concentration in the basal regions of the brain where the coccidioidal meningitis tends to localize.[19,20] Case 4 clearly shows the importance of intrathecal therapy in coccidioidal meningitis.

For intrathecal administration, the injection should be given alternately by lumbar, cervical (C1-C2) and cisternal punctures to minimize the magnitude of chemical arachnoiditis. Tolerance is better and symptoms of arachnoiditis are less when the drug is injected within the cisternal subarachnoidal space.[19,20] However, serious complications can occur. The senior author has done over 70 cisternal taps and two nearly fatal complications have occurred due to cisternal hemorrhage from needle trauma. The cardinal signs of these symptoms were as follows: Ten to 15 minutes after cisternal tap the patient suddenly experienced chills followed by occipital headaches, nausea, vomiting, profuse perspiration, hyperpyrexia, hypertension, tachycardia, rapidly shallow respiration, bilateral constricted pupils, decreasing level of consciousness and rapidly progressing deep coma. The CSF was grossly bloody and under notably elevated intrathecal pressure. Treatment consisted of immediate lumbar tap to remove enough fluid to bring the intrathecal pressure to the upper limits of normal, light sedation and complete bed rest. Soon after the intrathecal pressure dropped, the respiratory rate improved immediately and the patient regained consciousness within two to four hours. An emergency cerebral angiogram was done soon after the patient's condition stabilized to exclude the possibility of bleeding from other surgically correctable intracranial lesions. This complication should be kept in mind when a cisternal tap is carried out.

Except in Case 7 (in which there was preexisting severe liver disease), miconazole has not affected hepatic, renal or bone marrow functions in patients even after 4½ months of intravenous therapy in doses of 1,200 to 3,000 mg per day. No evidence of further deterioration of renal function has been observed in two patients with impaired renal function before miconazole therapy. In agreement with data in the literature, nephrotoxicity has not been observed.[21,22]

From our limited clinical experience, miconazole appears more effective when given intrathecally for fungal meningitis than when given intravenously for soft tissue fungal infections. The therapeutic concentration of the drug is higher and maintained longer in CSF after intrathecal administration than it is in serum after intravenous infusion, possibly because the drug is highly bound by plasma protein, while the protein concentration in the CSF is much less. Therefore, a higher bioactive concentration of the drug can be maintained in the CSF. Our impression is that miconazole is apparently an effective antifungal drug of low toxicity and is a potentially useful agent in the treatment of human systemic mycoses and fungal meningitis in particular.

Summary

Ten patients with systemic mycoses, after failing to respond to currently approved antifungal agents, were treated with intravenously administered miconazole. The maximum and minimum

serum concentrations of the drug were found to be at least 7.5 μg per ml and 0.4 μg per ml 15 minutes and 7½ hours after 800 mg of miconazole was given intravenously. Minimal inhibitory concentrations of miconazole for clinical isolates of Coccidioides immitis mycelium, Cryptococcus neoformans and Candida albicans were less than 0.6 μg per ml. Five patients with fungal meningitis received both intravenous and intrathecal therapy. CSF concentrations of the drug one hour after an intravenous infusion of 800 mg of miconazole were 0.1 μg per ml in four patients with coccidioidal meningitis and 0.3 μg per ml in one patient with cryptococcal meningitis. When 20 mg of miconazole was given intrathecally via lumbar injection in a patient with coccidioidal meningitis, 6.5, 2.4, 0.77 and 0.24 μg per ml of miconazole were found in the CSF at the cisternal level at 12, 24, 48 and 72 hours, respectively. In the four patients with coccidioidal meningitis, the CSF showed a decrease in cell count, protein and complement fixation antibody titer after intrathecal therapy. The yeast isolated from the one patient with cryptococcal meningitis was found to be resistant to 100 μg per ml of amphotericin B, but sensitive to less than 0.6 μg per ml of miconazole *in vitro*. The CSF cultures for Cryptococcus neoformans were continuously positive for six months while under amphotericin B and 5-fluorocytosine treatment, but became negative after nine days of intravenous and intrathecal therapy with miconazole. In patients with fungal meningitis there was better objective response to therapy with miconazole than other forms of dissemination.

No measurable impairment of renal, hepatic or bone marrow function was observed in patients after 4½ months of intravenous therapy in doses of 1,200 to 3,000 mg per day. No hematological or biochemical abnormalities were observed in 16 months of follow-up in our first patient treated with this drug.

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Medical
PROGRESS

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Cell-Mediated Immunity and Its Role in Resistance to Infection

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The recently acquired knowledge of the importance of cell-mediated immunity in many illnesses and the discovery of a variety of substances that can restore certain cell-mediated immune functions has served to focus the attention of physicians on this area of immunity. It is important for practicing physicians to have a clear understanding of current knowledge of the role of cell-mediated immunity in resistance to infection and how this arm of the immune system relates to the diagnosis and therapy of infectious diseases.

RECENT ADVANCES in treatment of patients with malignancies, collagen-vascular disorders and organ transplants have been accompanied by discouragingly high rates of infection. The defects in host defense which are frequently associated with these conditions, along with the profound immunologic abnormalities which result from the administration of newer immunosuppressive therapeutic regimens, have resulted in an increase in susceptibility to life-threatening infections in these patients—infections caused by a variety of opportunistic organisms. Great effort has been expended in studying persons with normal and compromised immunologic functions in order to discover means whereby immunologic defects might be prevented or overcome so as to lessen the frequency of infection.

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While it was suspected for years that a form of immunity mediated by cells was important in defense against certain infections, this hypothesis was not proven until Chase, in a series of classic experiments in guinea pigs, showed that lymphoid cells could successfully transfer cutaneous delayed hypersensitivity to tubercle bacilli from one animal to another.[1] Cutaneous delayed hypersensitivity (DH) is an inflammatory response that reflects the ability of the host's cellular immune system to respond to the eliciting antigen (organism). In more recent experiments, it has been shown that the lymphoid cells that are able to transfer protection against certain infectious agents are thymus-derived or T lymphocytes[2] (in contrast to B lymphocytes which are the cells responsible for antibody production). For example, thoracic duct lymphocytes transferred from animals immunized to Mycobacterium tuberculosis into unimmunized animals have been shown to confer protection to tuberculosis.[3] These experiments have allowed for a working definition of cell-mediated immunity (CMI) as that particular response of the immune system which requires previously sensitized thymus-derived lymphocytes and is independent of

ABBREVIATIONS USED IN TEXT

BCG = bacille Calmette Guérin
CMI = cell-mediated immunity
Con A = concanavalin A
DH = delayed hypersensitivity
LCM = lymphocytic choriomeningitis virus
MIF = migration inhibition factor
PHA = phytohemagglutinin
SKSD = streptokinase-streptodornase

circulating antibody. CMI has been found to be of major importance in resistance to a variety of facultative and obligate intracellular organisms (many of which persist and multiply within phagocytic cells of the reticuloendothelial system). Many of these organisms are opportunistic pathogens that infect immunocompromised hosts (Table 1). A role for CMI has also been elucidated in other important biologic processes such as rejection of allografts, resistance to tumor and graft-versus-host reactions. These will not be considered here.

CMI and humoral immunity may be operative, either together or singly, against any particular pathogen. Humoral antibody plays a major role in resistance against a number of microorganisms and their toxins, including such bacteria as Group A streptococci and Hemophilus influenzae, viruses such as influenza virus and poliovirus, and toxins from bacteria such as Corynebacterium diphtheriae and Clostridium tetani. Humoral immunity and CMI differ in many respects, and a number of these differences are given in Table 2.

In addition to specific antibody and CMI, a variety of nonspecific mechanisms such as the complement cascade and polymorphonuclear leukocytes have important roles in resistance to infection, but will not be considered here. This will not be a complete review but will focus on the mechanisms of CMI, the deficiencies in the functioning of CMI, and diagnostic and therapeutic implications.

Mechanisms of Cell-Mediated Immunity

The cell-mediated immune response to an organism is initiated when T lymphocytes are specifically sensitized by contact with its foreign antigens (afferent limb) (Figure 1). Contact between lymphocytes and antigen occurs either at the site of infection or in lymph nodes draining the peripheral area where the organism has invaded. In lymph nodes, T lymphocytes localize to and are sensitized in periarteriolar areas which are referred to as thymus-dependent areas. Two types of antigen stimulate T lymphocytes but not B lymphocytes: the first is certain small molecules such as arsenobenzoate-N-acetyl tyrosine or some synthetic peptide copolymers of tyrosine or glutamic acid; the second is larger molecules, only part of which are recognized as foreign, such as dinitrochlorobenzene complexed with skin protein.[4] Those antigens most likely to induce sensitization of T lymphocytes *in vivo* are proteins found on the membranes of living cells. Antigens on dead cells or antigens alone are less effective.

Macrophages, bone marrow-derived tissue

TABLE 1.—*Pathogens Against Which Cell-Mediated Immunity Appears to Be Important in Host Defense.*

Bacteria	*Viruses*	*Fungi*	*Protozoa*	*Helminths*	*Unclassified*
Mycobacteria, including M. tuberculosis and M. leprae	Herpes simplex	Aspergillus species	Toxoplasma gondii	Schistosome species	Pneumocystis carinii
Salmonella species	Herpes zoster	Candida species	Plasmodia species	? Strongyloides stercorales	
Listeria monocytogenes	Cytomegalovirus	Cryptococcus neoformans			
Francisella tularensis (Tularemia)	Rubeola (measles)	Phycomycetes species			
Brucella species	Vaccinia	Histoplasma capsulatum			
Treponema pallidum		Coccidioides immitis			
Malleomyces pseudomallei (Meliodosis)					
Malleomyces mallei (Glanders)					

TABLE 2.—*General Characteristics of Humoral and Cellular Immunity*

Characteristic	*Humoral Immunity*	*Cellular Immunity*
Time course for maximal effect	Minutes to hours	Usually days
Mediator cell	B lymphocytes and derived plasma cells	T lymphocytes
Effector	Antibody	Lymphocytes and macrophages
Active against	Extracellular pathogens	Intracellular pathogens

phagocytes, appear to play an early role in processing of antigens. In certain situations, antigens phagocytosed and then processed by macrophages and subsequently presented to T lymphocytes are more effective sensitizers of CMI than are the antigens alone. There is evidence that modification of antigens by a variety of means including processing by macrophages,[4] enzymatic degradation[5] and chemical alteration[6] changes antigens in such a way as to make them more immunogenic.

Within one or two days after exposure of T lymphocytes to antigen modified by macrophages or to antigen alone, a proportion of the exposed T lymphocytes undergoes a process known as transformation (Figure 2). This process produces specifically immune cells which are then able to mediate the functions of CMI *in vivo* and *in vitro*. These cells will be referred to as sensitized lymphocytes. The lymphocytes which transform enlarge, the nuclear material changes from heterochromatin to euchromatin, synthesis of ribonucleic acid (RNA), deoxyribonucleic acid (DNA) and protein increases, and the cells eventually undergo multiple divisions. Lymphocyte transformation may be monitored *in vitro* and *in vivo* by both morphologic changes and by quantitative demonstration of DNA synthesis (incorporation of radiotagged precursors of DNA). *In vitro,* T lymphocyte transformation may be induced not only by specific antigen but also by mitogens, such as concanavalin A (Con A) and phytohemagglutinin (PHA), which are lectins that bind to carbohydrates of cell membranes. *In vitro* lymphocyte transformation as a measure of CMI correlates with DH skin responses (such as to tuberculin or histoplasmin).

Once sensitized to antigen, T lymphocytes become the mediators of the effector limb of CMI (efferent limb), or may become long-lived "memory cells" (Figure 3). The "memory" T lymphocytes circulate in blood and lymphatics (T lymphocytes make up approximately 60 percent of circulating blood lymphocytes[7]) and are specifically committed—that is, they will respond only to that particular antigen to which they were previously exposed. They are responsible for the

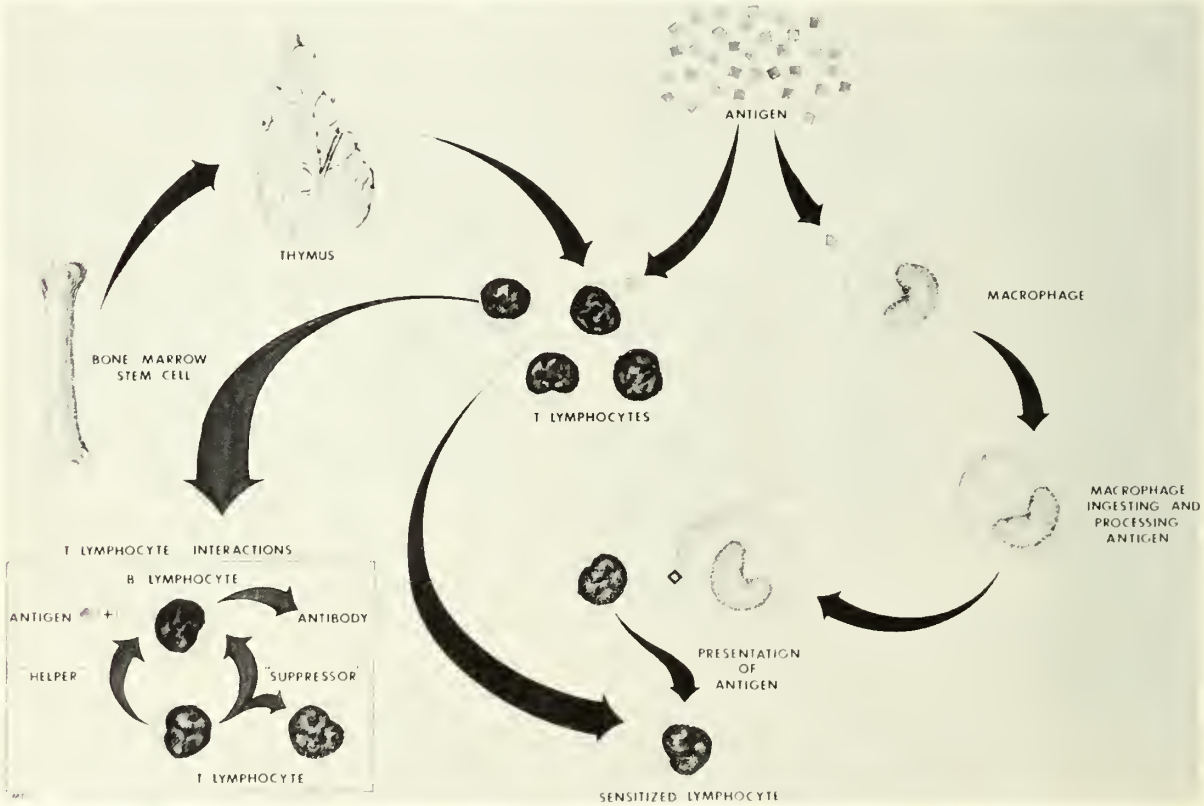

Figure 1.—Cell-Mediated Immunity—Afferent Limb. T lymphocytes are derived from bone marrow stem cells and are converted to T lymphocytes in the thymus gland. When exposed either directly to antigen or to antigen processed by macrophages, a proportion of T lymphocytes becomes sensitized—that is, have the potential to activate the efferent limb of cell-mediated immunity when reexposed to antigen (Figure 3). T lymphocytes may also regulate B lymphocyte production of antibody and may regulate the response of other T lymphocytes (insert).

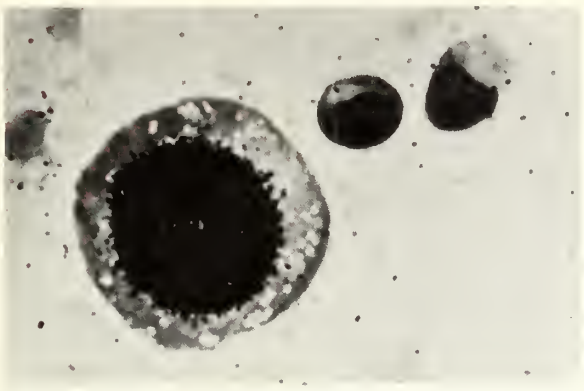

Figure 2.—Blast Transformation of Lymphocytes. Two resting human lymphocytes (right) are next to a lymphocyte stimulated by streptokinase-streptodornase undergoing blast transformation. The cells were pulsed with a radioactive precursor of DNA (^{3}H-labeled thymidine) and autoradiography was carried out. The nucleus of the transforming cell took up the ^{3}H-thymidine because of the rapid rate of DNA synthesis and appears blackened by the effect of the radioactivity on the emulsion. (X400)

heightened rapid response of CMI upon reexposure to the original sensitizing antigen.

After reexposure to an infectious agent (antigen), specifically sensitized T lymphocytes may function in several ways to protect the host. They may produce a variety of soluble substances referred to as lymphokines which can stimulate lymphocytes and phagocytic cells to establish an effective host defense. Most of these lymphokines and their functions have been shown *in vitro* only. Several of them are listed in Table 3. A blastogenic factor is one such product of sensitized lymphocytes exposed to antigen at a peripheral site. When released into the local area or into the systemic circulation, it may enhance transformation in other lymphocytes, thereby enhancing the overall immune response. Other lymphokines attract macrophages to the site of antigen (infection), inhibit macrophage migration from that site and activate the macrophages (Figure 3). In

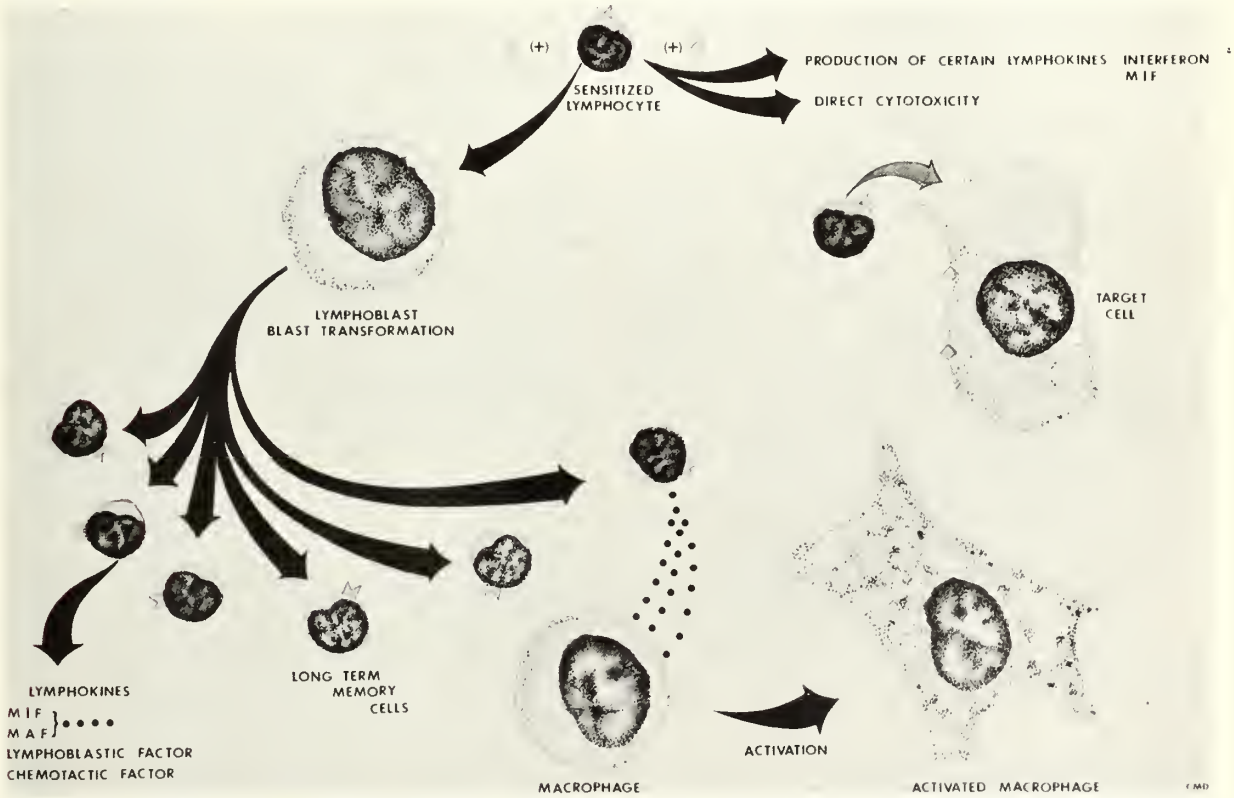

Figure 3.—Cell-Mediated Immunity—Efferent Limb. Sensitized T lymphocytes reexposed to the sensitizing antigen may undergo blast transformation and then proliferate. The subsequent progeny of sensitized lymphocytes may produce a variety of lymphokines which mediate the cellular inflammatory response. These lymphokines include migration inhibition factor (MIF) and aggregation factor (MAF) which may activate macrophages, chemotactic factor which attracts monocytes and macrophages, and lymphoblastic factor which stimulates other lymphocytes to undergo transformation. Some of these T lymphocytes may become long-term "memory" cells which circulate in blood and lymph and which remain sensitized for years. Sensitized T lymphocytes exposed to the appropriate antigen may also produce certain lymphokines (for example, MIF or interferon) without undergoing transformation or proliferation. These nontransforming cells may lyse target cells that have an appropriate antigen on their cell surface (such as viral).

this manner, major cell types necessary for effective resistance are mobilized and activated to destroy or at least contain the pathogen at the site of invasion. Examples of containment are the granulomas which form about tubercle bacilli, schistosome eggs and histoplasma. Interestingly, the production of many of these lymphokines, including interferon, is not necessarily correlated with blast transformation and some—such as migration inhibition factor (MIF)—may be produced by B lymphocytes as well as T lymphocytes.[8,9] T lymphocytes may also directly lyse host cells which are infected (for example, viral infected cells with viral antigen on their surfaces), thereby destroying the intracellular environment necessary for replication of the microorganism. Unsensitized lymphocytes in the presence of antivirus antibody have been shown to lyse these virus-infected cells as well.

T lymphocytes may have numerous other functions, including enhancement or suppression of antibody production by B lymphocytes and suppression of lymphocyte transformation by other T lymphocytes *in vitro*. Recently, evidence has been presented that a subpopulation of T lymphocytes is the factor responsible for depression of lymphocyte transformation in patients with disseminated fungal disease.[10]

In addition to the above functions, T lymphocytes are responsible for changing normal macrophages to activated macrophages. Normal macrophages are derived from bone marrow monocyte precursors which migrate via blood to tissue. Morphologically, these cells are characterized by their large size, spreading borders, abundant cytoplasmic granules and vacuoles, and their indented or multiple nuclei (Figure 4). They are motile and phagocytic and adhere to glass; they also have membrane receptors for certain subclasses of immunoglobulin G (IgG), immunoglobulin M (IgM) and complement. Normal macrophages ingest a variety of particulate materials, including pathogenic microorganisms, but their ability to kill these microorganisms varies considerably with the pathogen.

The activation of macrophages occurs through a specific immune process. Macrophages become activated when exposed to specifically sensitized lymphocytes plus the antigen to which the lymphocytes were previously sensitized or when exposed to certain substances such as bacterial endotoxin. These activated cells differ in certain respects from normal macrophages (Table 4) (Figure 4). The most important difference is their greatly increased capacity to inhibit or kill (efferent limb) intracellular pathogens. This effect appears to be nonspecific; thus, macrophages activated *in vivo* by lymphocytes exposed to one intracellular pathogen (such as Listeria monocytogenes) have the capacity to efficiently inhibit or kill unrelated intracellular pathogens, including bacteria such as Salmonella, viruses such as herpes simplex, fungi such as Cryptococcus neoformans and protozoa such as Toxoplasma gondii.[11] The presence of activated macrophages appears to be the most important factor in resistance to many infectious agents, including a number of those listed in Table 1.

Finally, as alluded to above, it has been recognized that synergistic interactions occur between humoral immunity and CMI. A particularly important aspect may be the enhancement of phagocytosis by macrophages which occurs when certain microorganisms such as Salmonella[11] are

TABLE 3.—*Some Products of Activated Lymphocytes*

Product	*Activity*
Affects lymphocytes	
Blastic factor	Induces normal lymphocytes to undergo blast transformation
Affects macrophages	
Migration inhibition factor (MIF)	Inhibits (and activates?) migration of macrophages
Aggregation factor (MAF)	Agglutinates macrophages
Chemotactic factor	Attracts macrophages and monocytes
Affects other cells	
Lymphotoxins	Lyse various cell lines in culture
Growth inhibitory factors	Prevent proliferation without damaging cells
Other	
Skin reaction factor	Causes indurated skin lesions
Interferon	Inhibits viral multiplication in cultured cells
Basophil and eosinophil chemotactic factor	Attracts basophils and eosinophils

coated with antibody. Although parasitized red blood cells may be destroyed by humoral factors or by macrophages from malaria-infected animals, antibody and macrophages together destroy malaria-infected red blood cells more quickly and more completely than either alone.[12] On the other hand, antagonism between humoral and cellular immunity has also been described[13,14]—for example, the DH skin response to a specific antigen may be blocked by antigen-antibody complexes in mice.

Evidence for the Role of CMI in Resistance to Infection

The most convincing evidence that CMI plays a major role in resistance to infection has come from experimental animal models of infections due to certain intracellular pathogens. Several examples of these are described in this section.

The classic model depicting the function of cellular immunity and its importance in bacterial disease is listeriosis in mice.[15,16] When a sublethal number of Listeria are injected intravenously into mice, the bacteria initially localize and multiply in the liver and spleen. After three days of logarithmic growth, the number of bacteria in these organs stabilizes and then decreases, and eventually the infection is eradicated. The mice are then resistant to an inoculum containing as many as 100 times the number of bacteria that cause death in 100 percent of mice. This remarkable resistance cannot be transferred with serum of immune mice but can be with their spleen cells. The appearance of specifically sensitized lymphocytes coincides with the appearance of DH to Listeria and with the eradication of bacteria from the tissues (Figure 5). Furthermore, nonimmune mice injected with sensitized lymphocytes from mice immune to Listeria—but not with lymphocytes from mice immune to other organisms, such as bacille Calmette Guérin (BCG)—are highly and specifically resistant to Listeria challenge. Previously committed T lymphocytes are the cells responsible for mediating the observed resistance and they do so by activating macrophages. Thus, both sensitized T lymphocytes and macrophages are necessary for proper functioning of resistance to Listeria. Macrophages obtained from the peritoneal cavities of animals infected two weeks earlier with Listeria have the properties of activated macrophages. Whereas Listeria are able to multiply in macrophages of normal mice, they are killed rapidly by macrophages of mice infected with Listeria. These activated macrophages have been shown to be present in the liver, spleen and peritoneal cavity at the time during the acute infection when the organisms are being eliminated from the liver and spleen (fourth day after infection). As discussed in the previous section, these activated macrophages in Listeria-infected animals have the capacity to inhibit or kill not only Listeria but a variety of other intracellular pathogens as well as to confer resistance *in vivo* to these unrelated

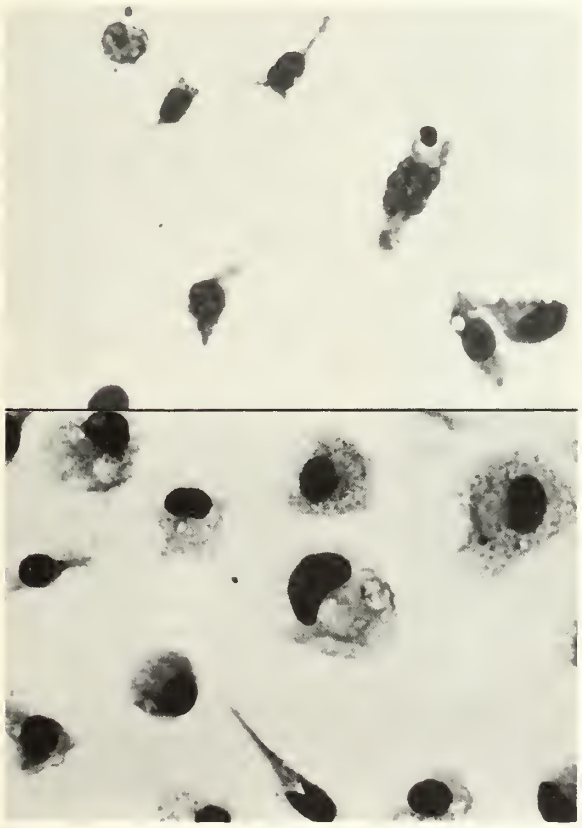

Figure 4.—Normal and Activated Macrophages. Upper, Normal macrophages are large mononuclear cells with cytoplasmic granules and vacuoles, indented or multiple nuclei, and spreading borders. **Lower,** Activated macrophages are larger, have more granules and vacuoles, spread more on glass, and have an increased capacity to kill microorganisms. (X160)

TABLE 4.—*Properties of Activated Macrophages*

Large size, more complex morphology
Increased spreading on glass; enhanced phagocytosis
Increased lysosomal hydrolase levels
Higher ratio of glucose metabolism by hexose monophosphate shunt as compared with glycolytic pathway
Increased digestive capacity, respiratory rate, and mitotic rate
Increased capacity to kill or inhibit replication of a variety of organisms

organisms. This ability of activated macrophages to kill completely unrelated organisms (such as protozoa and viruses) is why these cells are considered to represent the nonspecific effector arm of cellular immunity. This model, murine listeriosis, illustrates the essential role of CMI in resistance to intracellular bacterial infections in mammalian hosts as well as the interrelationships between the specific and nonspecific limb of cellular immunity (Figure 5).

It is important to realize that infection with intracellular bacteria may have at least three different outcomes depending on the infecting organisms and the response of the host. Macrophages may destroy all bacteria; the bacteria may be phagocytosed by macrophages but not be killed, resulting in dissemination and death of the host; or macrophages may not kill the pathogen, but they may limit multiplication and dissemination by granuloma formation (in tuberculosis, for example). To a large extent, therefore, resistance to intracellular bacteria depends on the presence of adequate numbers of activated macrophages that are able to kill or limit spread of the bacteria. As mentioned above, these findings are not unique to Listeria, but extend to many viruses, protozoa and fungi, as well as to other intracellular bacteria.

The important functional immune response to certain viral infections, particularly those in which

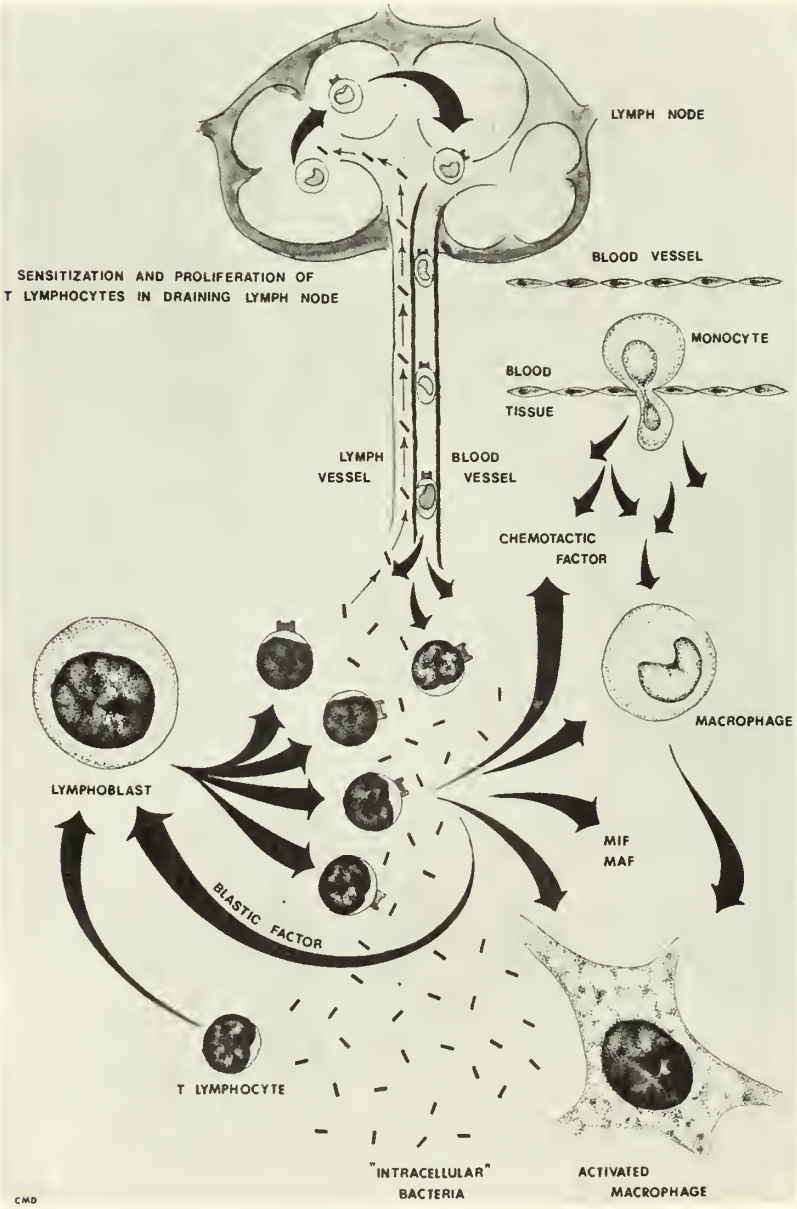

Figure 5.—Development of Resistance to Intracellular Bacteria. A proportion of lymphocytes in peripheral tissue exposed to intracellular bacteria undergo blast transformation and proliferation. Lymphocytes in draining lymph nodes may be exposed to antigens of the bacteria as well (via lymph channels) and undergo blast transformation and proliferation; they then return by the circulatory system to the site of antigen. Lymphocytes from both these sources produce lymphokines which attract other inflammatory cells (such as monocytes from blood). These lymphokines also serve to activate macrophages and induce other lymphocytes to undergo blast transformation. Activated macrophages ingest and kill the intracellular bacteria.

viral transmission occurs by cell to cell contact rather than by release of virus into the extracellular environment, appears to be cell-mediated.[17,18] For a particular virus, an individual function or a combination of functions of sensitized T lymphocytes may be important—such as (1) mobilization of macrophages; (2) direct cytotoxicity; (3) release of interferon. One particularly well-studied, illustrative model is ectromelia virus infection in mice,[19-22] an infection similar to smallpox in humans. Control of ectromelia virus multiplication in experimental infection begins four to six days after injection of the virus and coincides with the appearance of specific sensitized T lymphocytes. Immunity can be transferred by T lymphocytes but not by B lymphocytes, phagocytic cells, interferon or antibody. In tissue culture the sensitized T lymphocytes can directly lyse virus-infected cells, thereby destroying the intracellular environment necessary for multiplication of the virus.

In the ectromelia model, histologic preparations show that macrophages are attracted to sites of viral replication and resolution of foci of infections occurs only with the appearance of macrophages in these lesions. Elimination of either lymphocytes or macrophages allows dissemination of the virus and death of the host. Therefore, it appears that both sensitized lymphocytes and macrophages are necessary for recovery from this virus infection.

In systems in which previously sensitized T lymphocytes are able to lyse virus-infected cells, it is of interest that antibody to the virus blocks the cytotoxicity (presumably by shielding the antigen from recognition by the cytotoxic T lymphocyte).[23] Recent data indicate the existence of other mechanisms for sensitization and cytotoxicity of CMI against virus-infected cells. Nonimmune mononuclear cells (probably macrophages) lyse herpes virus-infected cells in the presence of serum with high titers of antibody against herpes virus.[24,25] In this situation, antibody may increase the cell to cell contact between macrophage and virus-infected cell. A second mechanism has been described in cells infected with lymphocytic choriomeningitis virus (LCM). The virus seems to change a normal antigen, the H-2 histocompatibility antigen, on the membrane of infected cells. This altered antigen is recognized as foreign by host lymphocytes which then lyse the infected cells.[26,27]

Cytotoxicity, or direct killing of host cells by T lymphocytes, may be beneficial, as in the ectromelia model, or may be detrimental, as illustrated by the model of LCM infection in mice.[23] In this infection, T lymphocytes are sensitized by LCM-infected cells and are then directly cytotoxic for these cells. This cytotoxicity of the lymphocytes is actually detrimental to the infected host because the cytotoxicity is directed against vital tissues—the meninges, ependyma and choroid plexus. The virus by itself does not appear to directly harm the infected tissue. Thus, viral infections may induce cytotoxicity to virus-infected host cells by an immunologic mechanism; this cytotoxicity destroys virus by destroying tissue. Benefit to the host occurs if this destructive process does not compromise function of a vital organ or tissue.

In response to infection by virus, interferon is produced by numerous cell types, including macrophages and lymphocytes.[18] This protein may bind to host ribosomes and by preventing translation of viral RNA it can prevent viral multiplication and thereby spread of virus.[28] In tissue culture, interferon decreases direct viral cytotoxicity. In animal models the levels of circulating interferon correlate with improvement in certain viral infections, and in man local interferon levels correlate with clinical recovery in humans infected with varicella-zoster.[29]

In general, cellular immunity in infections other than those caused by viruses and bacteria has been less clearly characterized. There is indirect evidence which suggests an important role for CMI in human fungal infections.[30,31] For instance, patients with underlying defects in CMI, but normal humoral immunity, such as those with chronic mucocutaneous candidiasis or Hodgkin's disease, are abnormally susceptible to disseminated fungal infections. Iatrogenic immunosuppression, which affects cellular immunity more than humoral, as in regimens administered to patients with renal or cardiac transplants, has resulted in a remarkable incidence of fungal disease. Evidence for a role for CMI derived from experimental fungal infections in animals is less convincing and consequently the relative importance of humoral immunity versus CMI has yet to be elucidated.

In protozoal infections, such as malaria and toxoplasmosis, both CMI as well as humoral antibodies may be important in overall resistance to infection caused by these organisms. In experimental malaria, manipulations which deplete thymus-dependent cells exacerbate infection; transfer of specifically immune lymphocytes con-

TABLE 5.—*Congenital Disorders of Cell-Mediated Immunity*

	Thymic hypoplasia (DiGeorge syndrome)	*Autosomal recessive Lymphopenia (Nezelhof syndrome)*	*Cartilage hair hypoplasia*	*Chroric mucocutaneous candidiasis*	*Immunodeficiency with thrombocytopenia (Wiskott-Aldrich syndrome)*	*Ataxia telangiectasia*	*Combined deficiency disease*
Increased incidence of infection to:							
Intracellular bacteria	..	yes	..	..	..	..	yes
Viruses	yes	yes	yes	..	yes	yes	yes
Fungi	yes	yes	..	yes	..	..	yes
Protozoa	yes	yes		..	yes	..	yes
Lymphopenia	yes	yes	yes	variable	variable	variable	yes
Absent delayed-type hypersensitivity	yes	yes	variable	variable	variable	variable	yes
Absent lymphocyte transformation to phytohemagglutinin (PHA)	yes	yes	variable	variable	variable	variable	yes
Absent lymphocyte transformation to antigen	yes	yes	yes (Varicella)	variable	variable	variable	yes

fers protection to infection in some models, but transfer of serum also confers some resistance.[32] Most likely both antibody and cells play a role in resistance to malaria (see also under Mechanisms of Cell-Mediated Immunity above).

Similarly, in murine toxoplasmosis, acquisition of resistance after infection is correlated with the appearance of specifically immune lymphocytes, activated macrophages and serum antibody.[33-35] Transfer of spleen cells specifically immune to Toxoplasma to unimmunized animals confers protection to infection.[36] Macrophages from animals chronically infected with Toxoplasma are activated and have the capacity to kill Toxoplasma, whereas macrophages from normal mice support growth of this organism.[37] Toxoplasma infection also induces humoral antibodies of both IgM and IgG classes and these contribute to protection against infection.[38]

Evidence that CMI plays an important role in other protozoal infections, such as trypanosomiasis and leishmaniasis, is beginning to accumulate,[32] but will not be discussed here.

The role of immunity in protection against most metazoan parasites is poorly understood. For instance, an intensively studied trematode parasite, Schistosoma, elicits both humoral and cellular immunity.[39] Protection against reinfection after initial exposure, however, has been consistently shown only in a few of the many animal models studied. Artificial alteration of the immunologic system of the host has no effect on development of protection.[40] Transfer of immunity to schistosomiasis either by cells or by serum has not been convincingly shown. Altering CMI prevents granuloma formation around schistosomal eggs[39] and causes more severe infection.[41,42] Other factors just beginning to be explored, such as the role of eosinophils[43] and IgE antibodies,[44] may play significant roles in schistosomiasis. In one system, however, the immunologic factors necessary for recovery from a metazoan parasite have been delineated. It has been shown that elimination of the rat nematode infection caused by Nippostrongylus brasiliensis requires both antibody and cells.[45]

Defective Functioning of Cell-Mediated Immunity

Functional impairment of CMI may result from defects in any or all elements of this arm of the immune system. This impairment may be beneficial—for example, by enabling survival of renal

or cardiac transplants—or detrimental—for example, by increasing susceptibility to infection and to development of tumors. This section will briefly describe some of the major congenital and acquired defects in CMI which may lead to increased susceptibility to infection.

A number of congenital disorders of CMI and their associated laboratory abnormalities are listed in Table 5. Congenital thymic hypoplasia or DiGeorge syndrome, a classic example of a disease with defective CMI, results when the third and part of the fourth pharyngeal pouch fail to develop during embryogenesis. This failure of development results in absence of the thymus and parathyroid glands.[46] Severe hypocalcemia and tetany secondary to hypoparathyroidism occur in the neonatal period and are early clues to the diagnosis. Absence of the thymus gland prevents differentiation of lymphocyte precursors into T lymphocytes; this lack of T lymphocytes prevents expression of the normal cellular immune response. Children with this disorder are lymphopenic, and thymic dependent areas of lymph nodes show depletion of lymphocytes. Lymphocytes do not undergo transformation when exposed to either mitogen or antigen or when placed in mixed lymphocyte culture (a reaction in which lymphocytes with one type of histocompatibility antigens become sensitized to lymphocytes with different histocompatibility antigens and consequently undergo transformation). Production of lymphokines such as MIF is lacking. DH skin reactivity is absent; these patients do not react to skin testing with antigens such as streptokinase-streptodornase (SKSD) and candidin, and they cannot be sensitized with the potent artificial inducer of DH, dinitrochlorobenzene. The defects in these aspects of CMI are paralleled by a life-threatening susceptibility of these patients to pathogens such as Pneumocystis carinii, Candida albicans, herpes simplex virus and varicella-zoster virus.[46,47] They are not susceptible to organisms against which antibody and neutrophils are the primary defense mechanism. If these children survive neonatal hypocalcemia, they frequently succumb to overwhelming infection.

Other congenital diseases that effect CMI are associated with variable defects in resistance to intracellular pathogens (Table 5). One important clinical corollary in the management of patients suspected or known to have disorders of CMI is the danger associated with their receiving live vaccines such as BCG, vaccinia, measles and mumps. The attenuated organisms in these vaccines are handled easily by the immune system of normal patients but may disseminate with fatal consequences in patients with defects in CMI.

Among the acquired conditions that may cause depression of CMI function is infection itself. Those infections known to depress DH skin tests are listed in Table 6. Depression of *in vitro* lymphocyte transformation to either mitogens or antigens is associated with viral infections such as influenza and infectious mononucleosis, live vaccines such as measles-mumps-rubella and rubella, bacterial infections such as tuberculosis, leprosy, syphilis and bacterial pneumonia, and fungal infections such as coccidioidomycosis. Although most studies of depression of CMI during infections have concentrated on showing defects in DH skin testing and lymphocyte transformation to both mitogens and antigens, a recent report describes suppressed chemotaxis of monocytes from patients with acute influenza.[48] This suppression of chemotaxis persists for approximately three weeks and can be reproduced in monocytes of uninfected persons by infecting their monocytes with influenza virus. Therefore, both lymphocyte and monocyte function may be abnormal during and after acute infections. It is unclear whether depression of these *in vivo* and *in vitro* correlates of CMI by a given infection results in an increased susceptibility to other organisms. For instance, in disseminated tuberculosis and coccidioidomycosis, it is unclear whether the defect in CMI is only a manifestation of the severity of the disease or whether it also predisposes to dissemination of the infection.

An interesting example of an infection which induces immunosuppression is measles. As early

TABLE 6.—*Some Infections and Vaccines Which May Be Associated with Depressed Delayed-Type Hypersensitivity*

Viral	*Bacterial*
Measles (and vaccine)	Tuberculosis
Mumps	Leprosy
Chicken pox	Syphilis
Influenza	Streptococcal infection
Infectious mononucleosis	Brucellosis
Yellow fever	Bacterial pneumonia
Rubella vaccine	Typhoid fever
Measles-mumps-rubella vaccine	
Other	*Fungal*
Schistosomiasis	Coccidioidomycosis
Toxoplasmosis	Histoplasmosis
	Blastomycosis

as 1908 it was recognized that acute measles infection was associated with a diminution or disappearance of preexistent cutaneous DH to tuberculin.[50] These observations have been extended more recently with the demonstration of the immunosuppression which occurs following administration of live, attenuated measles vaccine. Loss of DH skin test reactivity to tuberculin, candidin and dinitrochlorobenzene for one to four weeks is observed following vaccination, and lymphocytes from these patients show depressed responsiveness to tuberculin and candidin.[51] B lymphocyte function does not appear to be depressed by measles vaccine.

There are three postulated mechanisms for the immunosuppression which follows infection with virus or vaccine. After influenza infection, either with wild virus or vaccine, there is a significant decrease in the number of circulating T lymphocytes; this may represent one mechanism of depressed lymphocyte transformation in patients with infection. In another viral infection, rubeola, *in vitro* lymphocyte transformation to unrelated antigens is notably depressed if measles virus is added to the lymphocyte culture. This appears to be due to the fact that measles virus has a predilection for infecting transforming lymphocytes (as opposed to intermitotic lymphocytes). The virus may interfere with DNA synthesis of the transforming lymphocyte and thereby suppresses lymphocyte transformation and proliferation.[52] Such a mechanism could be caused by any virus which proliferates in transforming lymphocytes. A second postulated mechanism for lack of responsiveness of CMI after measles infection is competition between the antigen of the test system (such as tuberculin) and measles virus antigen for membrane receptors on sensitized lymphocytes. When tuberculin and either measles antigen or measles virus are added to lymphocytes from tuberculin positive patients, depression of lymphocyte transformation is noted, which depends on the concentration of both antigens.[53] Therefore, three phenomena—reduction of the number of T lymphocytes, infection of transforming lymphocytes and antigenic competition—are postulated to account for the immunologic depression observed during viral infections.

These abnormalities in tests of CMI during measles infection and their possible clinical relevance have been controversial. A contested issue is whether measles predisposes to an increased incidence of primary tuberculosis or to exacerbation of active tuberculosis. In one report, a pronounced increase in the incidence of new cases of pulmonary tuberculosis was said to have occurred in an epidemic of measles in Greenland in 1951.[54] In another, the clinical course of untreated pulmonary tuberculosis in children was stated to have worsened during measles infection.[55] In contrast, a measles epidemic in a tuberculosis hospital among children with active tuberculosis was studied and no evidence for exacerbation was noted.[56]

A major class of disorders which adversely affect both humoral and cellular immunity are the malignancies. For instance, multiple myeloma, a B lymphocyte malignancy, may be associated with both profound deficiencies of normal immunoglobulins and with large concentrations of homogeneous (monoclonal) gammaglobulin or its subunits (heavy chains or light chains) or both. Hodgkin's disease, on the other hand, is an example of a malignancy of the reticuloendothelial system with adverse effects on T lymphocyte function and depression of the manifestations of CMI. In patients with Hodgkin's disease, general lymphopenia is noted which is more severe with more diffuse disease.[57] This deficiency of lymphocytes and the defect in lymphocyte function seen in this disease are clearly reflected in studies in which such patients are skin tested to a battery of specific antigens. In only 34 to 66 percent of untreated patients with Hodgkin's disease are results positive to at least one antigen whereas there is response in 100 percent of normal persons. In addition, whereas only 45 to 67 percent of the patients with Hodgkin's disease can be sensitized to dinitrochlorobenzene, 96 percent of normal people can be sensitized.[57,58] Whether the incidence of impaired DH correlates with the stage of disease is controversial. It is important to recognize that radiotherapy and chemotherapy cause profound depression of lymphocyte transformation so that evaluation of such patients after therapy has begun is of little help in determining immunologic competency and its relation to Hodgkin's disease.[59]

The abnormality in DH in patients with Hodgkin's disease is correlated with diminished *in vitro* lymphocyte transformation to antigens, mitogen and in mixed lymphocyte culture. However, there seems to be a subpopulation of patients who have depressed DH but normal *in vitro* lymphocyte transformation to PHA.[60] The depression of lymphocyte function due to Hodgkin's disease is not

well understood but is attributed variously to serum factors[61-63] or to an adherent nonphagocytic mononuclear cell population.[64] Another *in vitro* measure of CMI in Hodgkin's disease, the production of the lymphokine, chemotactic factor, is normal, even when PHA responsiveness is abnormal.[65] However, levels of a naturally occurring chemotactic factor inactivator are detected in sera of patients with Hodgkin's disease, a factor which may result in a generalized defect in the ability to mobilize inflammatory cells in these patients.[66]

The abnormalities in CMI described above are associated with an increased susceptibility of patients with Hodgkin's disease to certain intracellular pathogens including herpes zoster virus, Cryptococcus neoformans,[67] Brucella,[68] Mycobacterium tuberculosis,[69] Listeria monocytogenes,[70] Salmonella[71] and Toxoplasma gondii.[72,73]

While defects in cellular immunity have been clearly established in Hodgkin's disease and certain other lymphomas, defects are less well described in other malignancies. Some advanced neoplasms such as pulmonary malignancies[74] and intracranial tumors,[75] are associated with depressed DH and mitogen-stimulated lymphocyte transformation. Failure of patients with solid tumors to be sensitized to dinitrochlorobenzene is also observed.[76] Findings in certain studies in animals show a soluble factor which is produced by tumors and which depresses macrophage-mediated resistance to infection.[77] Nonetheless, results of testing of CMI in many patients with malignancies other than those of the reticuloendothelial system who have not been immunosuppressed by cytotoxic drugs are entirely normal.[76]

Cytotoxic drugs and corticosteroids may have profound effects on both humoral and CMI response (Table 7). Defects in host defenses not associated with specific immunity may also occur; for instance, mortality rates secondary to infections in patients with acute leukemia are directly correlated with the severe neutropenia which results from these agents. Cytotoxic drugs usually affect cellular and humoral immune systems to different degrees.[78] Two chemotherapeutic drugs that are highly immunosuppressive, cyclophosphamide and methotrexate, differ both qualitatively and quantitatively in their effects on the immune system and will be used here as examples. Cyclophosphamide is a cycle-specific agent which is toxic to cells in either proliferating or resting stages but has a preferential effect on proliferating cells. Cyclophosphamide inhibits T lymphocyte proliferation as well as the production of many lymphokines.[79] It also depletes the intermitotic circulating T lymphocyte pool, thereby decreasing the number of both previously committed lymphocytes as well as those available for sensitization. Cyclophosphamide is thus able to suppress the immunologic response to a particular antigen, regardless of whether the host had been previously sensitized or not.[80] As might be expected, profound effects on antibody forming cells also occur upon exposure to this drug.

Methotrexate, on the other hand, is a phase-specific drug which acts only on dividing cells. If the drug is administered for seven days after an animal is exposed to a new antigen, depression of DH and antigen-specific lymphocyte transformation occurs. If it is administered before or after the seven day induction period, no effect on CMI function or on the number of T lymphocytes in the circulating pool is seen.[80] Therefore, methotrexate usually will not affect the CMI response to an antigen when sensitization has already been established.

Corticosteroid administration results in lymphopenia and shrinkage of organs of the reticuloendothelial system in certain animals such as mice. It has been realized, however, that there are large species differences with regard to susceptibility to corticosteroids—a fact that has generated considerable confusion in the literature. Man is relatively insensitive to corticosteroids; the principal effect of administration of the drug is to cause transient lymphopenia (24 to 48 hours).[81] In humans, this lymphopenia appears to be due to redistribution of lymphocytes of all types (T, B and null lymphocytes) to sites outside of the intravascular space and not to lysis of lymphocytes. Corticosteroids decrease expression of DH, possibly by decreasing access of lymphocytes to

TABLE 7—*Some Chemotherapeutic Agents and Their Effects on the Immune System**

Agent	*Inhibition of Primary Antibody Response*	*Inhibition of Cell-Mediated Immunity*
Cyclophosphamide	3+	3+
6-mercaptopurine	2+	2+
Methotrexate	2+	2+
Cytarabine	+	±
Vinca alkaloids	±	±
Dactinomycin	±	±
L-asparaginase	+	+
Procarbazine	2+	2+

*Adapted from Bodey et al: Postgrad Med 58:67, 1975

antigenic sites. Significant reduction of lymphocyte transformation and production of lymphokines probably does not result from administration of corticosteroids. But, interestingly, the action of certain lymphokines may be inhibited by this class of drugs; for instance, they block the effect of MIF on monocytes and macrophages.[82] Also, corticosteroids may protect the target cells from direct cytotoxicity by T cells, without directly affecting T lymphocytes themselves.[83]

Monocytopenia results from corticosteroids, presumably due to decreased release of monocytes from bone marrow and from movement of monocytes from the intravascular space. Monocytes are also adversely affected by corticosteroids, in that these agents cause a decreased clearance of particulate material and decreased bactericidal and fungicidal activity in monocytes *in vitro*.[84] Therefore, corticosteroids may affect the function of both lymphocytes and the monocyte-macrophage system in humans. Increased susceptibility to infection in animals, as well as an increased risk of reactivation of latent infections, can result from this class of drugs.[85] Although this is true also in man, this incidence will depend in large part on the underlying disease for which the corticosteroids are being administered. In general, these drugs do not increase the incidence of infection in humans significantly.[86]

Cytotoxic agents and corticosteroids are frequently administered in combination and it is the total effect of all drugs in the regimen that dictates the degree of immunosuppression. Studies with drug combinations in the treatment of malignancy in humans show there to be immunosuppression during therapy but return of immunologic competency after cessation of therapy. Continuous therapy has longer, more profound effects than does intermittent therapy.[78]

As would be expected from the above, when immunosuppressive agents are given before or simultaneously with experimental infections, DH fails to develop and mortality frequently increases. For instance, in mice, vinblastine sulfate, which irreversibly blocks cell division at metaphase, if administered 12 hours before to 24 hours after injection of Listeria, prevents development of a cellular immune response. Foci of infection which are infiltrated with macrophages in untreated mice are acellular in mice treated with vinblastine. Bacterial multiplication continues in the lesions of the latter mice without abatement and dissemination occurs.[87] Numerous other experimental infections produced by intracellular pathogens are exacerbated by immunosuppressive agents. Two examples are experimental tuberculosis in which DH is blocked and the infection is worsened by methotrexate,[88] and Candida albi-

TABLE 8—*Other Conditions Associated with Abnormalities of CMI*

Condition	*Abnormality*
Malnutrition and low birth rate in children[102-105]	Depressed DTH, LT, increased susceptibility to infection
Diabetes mellitus[106,107]	Depressed DTH, LT, granuloma formation, increased susceptibility to infection
Uremia[108,109]	Depressed DTH, LT, GVH
Age[110-113]	Depressed DTH, lymphocyte cytotoxicity, allograft rejection, MLR
Surgical operation and anesthesia[113,114]	Depressed LT, MLR, DTH, increased susceptibility to infection
Heroin addiction[115]	Depressed LT
Sarcoid[116]	Depressed DTH, LT

CMI = Cell-mediated immunity
DTH = Delayed-type hypersensitivity
LT = Lymphocyte transformation
GVH = Graft versus host
MLR = Mixed lymphocyte reaction

TABLE 9.—*Skin Test Antigens Commonly Used for Diagnosis of Infectious Diseases*

Disease or Organism	*Name of Antigen or Test*	*Time of Reaction*
Coccidioidomycosis	Coccidioidin	24-48 hr
	Spherulin	24-48 hr
Histoplasmosis*	Histoplasmin	24-48 hr
Mycobacterium tuberculosis	Purified protein derivative (PPD)	24-48 hr
Atypical mycobacteria†	PPD-A, PPD-B, PPD-G, PPD-Y	24-48 hr
Lymphogranuloma venereum	Frei test	24 hr
Mumps	Mumps antigen	24 hr

*Serology should be drawn before skin testing
†The usefulness of skin tests for diagnosis of infection with atypical mycobacteria has been questioned. Antigens are not generally available.

cans infection of mice in which corticosteroids increase mortality.[89] In humans, there is evidence for increased susceptibility to infection with the use of cytotoxic drugs. In children with acute lymphocytic leukemia, the incidence of Pneumocystis carinii pneumonitis increases when the number of cytotoxic agents used to combat the leukemia is increased.[90] Also, in patients with herpes zoster and stage III and IV lymphoma, a randomized trial suggests that treatment with cytosine arabinoside increases the time to resolution of zoster lesions. The antiviral effects of the drug are apparently less important than its immunosuppressive effects.[91]

Radiation affects proliferating and nonproliferating lymphoid cell populations and consequently depresses CMI.[92] In animals, depression of established DH and interference with initial sensitization of lymphocytes occurs as a result of radiation.[93] Susceptibility of animals to infection by such organisms as Listeria monocytogenes and Francisella tularensis is increased after exposure to continuous low dose gamma radiation.[94,95] Radiation plus agents such as cortisone and nitrogen mustard are more likely to result in relapse of latent infection than radiation or drug alone.[85] Extrapolation of these findings to humans is difficult because of the differences in radiation doses given to humans and to experimental animals and because of the deficiencies in CMI secondary to the underlying disease process in humans for which the radiation is being administered.[96]

Other drugs are associated with abnormalities of *in vitro* and *in vivo* functions of CMI including rifampicin[97,98] and niridazole, an antischistosomal drug.[99,100] The relevance of these abnormal CMI functions to susceptibility to infection is unknown at this time.

Antilymphocyte serum, which has proved useful in prolonging allograft transplants, destroys lymphocytes in the circulating pool leading to lymphopenia and abnormalities in the function of CMI.

In addition to those discussed, leukocytosis, anemia and fever depress DH skin responses.[101] A variety of other conditions are associated with abnormalities of CMI, some of which are listed in Table 8.

Diagnostic and Clinical Considerations

Delayed hypersensitivity skin tests which measure the response of a host to antigens of a particular pathogen can be useful in diagnosis of infectious diseases (Table 9). Absence of skin reactivity to these antigens may indicate either lack of previous exposure to the antigen, defect(s) of CMI, failure to properly inject the antigen intradermally or a defect in the ability of the host to develop nonspecific inflammatory skin responses (this latter defect can be tested by placing irritating substances such as benzalkonium chloride on the skin).

A brief outline of important considerations in the evaluation of patients with suspected defects in CMI is given in Table 10. Tests of the overall function of CMI include DH skin tests to antigens against which most people are sensitized, such as streptokinase-streptodornase (SKSD), mumps antigen, candidin and trichophyton. Almost 100 percent of normal adults will respond to at least one of these antigens. If these fail to elicit a response, sensitization of the patient may be attempted with a chemical such as dinitrochlorobenzene;[118] successful sensitization with this agent represents the ability of the CMI system to respond to new antigens. If there is no response to these tests, the patient may have a significant defect in CMI. For any skin testing, an initial evaluation should be

TABLE 10.—*Evaluation of Cell-Mediated Immunity**

History
- Increased frequency and severity of infections
- Abnormal response to live vaccines (e.g. Vaccinia)
- Frequent infections with less common pathogens (e.g. fungi)
- Recurrent diarrhea
- Family history of increased susceptibility to infection

Physical Examination
- Signs of chronic infection
- Absence of lymphoid tissue
- Signs associated with specific immunodeficiency disorders (see Table 5)

Laboratory
- Peripheral blood lymphocyte count (should be greater than 1200/cu mm) and morphology (presence of small lymphocytes [T lymphocytes])
- Cutaneous delayed hypersensitivity response to antigens (mumps, Candida, PPD, SKSD) and dinitrochlorobenzene (DNCB)
- Quantitation of T lymphocytes (e.g. sheep red blood cell rosetting)
- Chest x-ray for presence of thymic shadow in children
- Response of lymphocytes in vitro to mitogens, specific antigens, and allogeneic cells
- Lymphokine production (e.g. MIF)
- Lymph node biopsy
- Rejection of allogeneic graft

PPD = purified protein derivative
SKSD = streptokinase-streptodornase
MIF = migration inhibition factor

*Adapted after Gelfand et al[117]

made at two to six hours after injection of antigen for immediate hypersensitivity reactions which are not CMI responses and may result in false positive readings 24 to 48 hours later.

In vitro tests of CMI function are usually carried out only by specialized laboratories. Tests which may provide information regarding a specific defect of CMI in immunodeficient patients include quantitation of T and B lymphocytes in peripheral blood, ability of blood lymphocytes to undergo transformation to mitogens or specific antigens (such as SKSD) and production of lymphokines such as MIF. In certain conditions associated with a defect in CMI, there may be a dichotomy between the DH response *in vivo* and results of *in vitro* correlates of DH (for example, mucocutaneous candidiasis).

Enhancement of CMI in order to increase resistance to pathogenic microorganisms has been attempted, but success has been limited. Some of the more promising agents with potential for enhancing nonspecifically the immunologic response of a host and thereby increasing resistance to or combating already existing infection are discussed below. Corynebacterium parvum (killed) and BCG (live or various extracts) appear to stimulate both afferent and efferent limbs of CMI. The effect of these adjuvants may result from the stimulatory effect they have on macrophages. The function of macrophages in both the afferent limb (Figure 1) and the efferent limb (Figure 3) of the immune response are enhanced by these adjuvants. Adjuvants produce significant protection against certain infections in experimental animals,[119] but similar studies in humans have not been conducted.

Transfer factor is a relatively small molecule found in circulating human leukocytes that can transfer to nonimmunized persons the pattern of DH and presumably the immunologic competence of the donor. This effect may last for weeks or even years. Restoration of both DH and of the production of lymphokines, as well as clearing of chronic infections, occurs in some patients with congenital immunologic deficiencies, such as Wiscott-Aldrich syndrome[120] and chronic mucocutaneous candidiasis.[121] Transfer factor has been tried in numerous patients with a variety of infectious diseases (coccidioidomycosis, for instance) in an uncontrolled manner; conclusions regarding this form of therapy in infectious diseases must be reserved until properly controlled studies are carried out.[122]

Levamisole is an antihelminthic drug that also enhances CMI *in vitro* and *in vivo*. Levamisole restores responsiveness to dinitrochlorobenzene in anergic patients with malignancies[123] and restores responsiveness to tuberculin in elderly patients with depressed DH to this antigen.[124] The drug also enhances lymphocyte transformation to specific antigens in certain situations. Whether levamisole enhances macrophage functions such as phagocytosis *in vitro* and *in vivo* is controversial.[125,126]

There is evidence from a double-blind controlled trial in children with recurrent upper respiratory tract infections that levamisole treatment significantly reduces the number, duration and severity of infections compared with placebo.[127] Uncontrolled trials indicate that the drug may be useful in patients with recurrent aphthous stomatitis and recurrent herpes simplex infections.[128,129] More controlled clinical trials are needed to definitively determine the effectiveness of this drug to the above infections, as well as to other infections.[130]

Interferon, which was discussed above under the section on Evidence for the Role of CMI in Resistance to Infections, appears efficacious in certain viral infections. High doses of interferon given to humans experimentally exposed to rhinovirus 4 (a common cause of upper respiratory tract infection) prevents symptoms of infection and virus shedding.[131] However, interferon must be given one day before and continued for three days after challenge with rhinovirus to produce the protective effect. In addition, the high doses necessary to produce this effect are currently prohibitively expensive. Human leukocyte interferon given to patients with chronic hepatitis B and chronic active hepatitis causes Dane particles, which most likely represent complete hepatitis B virus, to disappear from the blood.[132] Repeated administration results in disappearance of the Dane particle for prolonged periods. Interferon has also been used in the treatment of herpetic keratitis[133,134] and cytomegalovirus infections[135,136] but without evidence of efficacy. Other trials of the use of interferon in viral infections are currently in progress.[137] Inducers of interferon have also been used in man. Preliminary clinical trials indicate that these agents may prevent or reduce rhinovirus infections.[138]

The thymus gland and its products appear to play an important role in establishing immunocompetence and possibly in regulation of CMI.[139]

Thymus gland transplants in selected patients with DiGeorge syndrome successfully restore immunocompetence.[140-142] In addition, a variety of cell-free extracts of thymus gland have the ability to restore immunocompetence to neonatally thymectomized animals and to accelerate maturation of CMI.[139] Thymosin, a product of the thymus gland which has been detected in the peripheral circulation, is a protein with a molecular weight of 12,200 and a known amino acid sequence. This thymic product enhances lymphocytopoiesis, restores immunologic competence in certain situations and enhances expression of T lymphocyte function *in vitro* and *in vivo*.[49,139,143]. The potential for the use of thymosin in treating both congenital and acquired deficiencies in CMI appears great, although controlled trials have not been carried out. Continued support for research in this area is critical if we are to seek to prevent or control infection in the immunosuppressed host.

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Diet and Diabetes

. . . Greater emphasis should be put on diet as a first treatment for maturity onset diabetes. After all, this was always the basis of therapy for diabetes. Before insulin came into effect 55 years ago, diet was the only thing that we had, and we must go back to diet.

—STANLEY N. COHEN, MD, *Philadelphia*
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Specialty Conference

Moderator

PHYLLIS A. OILL, MD

Discussants

STEPHAN R. TARGAN, MD
NORMAN M. PANITCH, MD

This is a transcript of one of the regular teaching conferences in Infectious Diseases held weekly at Harbor General Hospital, Torrance, California. These conferences have been edited by Doctors Anthony W. Chow, Thomas T. Yoshikawa, Phyllis A. Oill and Lucien B. Guze.

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Infectious Disease Emergencies

PART IV:

Patients Presenting with Gastrointestinal Disorders

PHYLLIS OILL, MD:* This part of the symposium on Infectious Disease Emergencies is concerned with those infectious processes that primarily are referable to the gastrointestinal tract. Dr. Stephan Targan will discuss the infectious diarrheal syndromes associated with dehydration and electrolyte abnormalities. Dr. Norman Panitch will then speak about mediastinitis and peritonitis. Table IV-1 is a compilation of the infectious disease entities that are related to this area of discussion.

Infectious Diarrheal Emergencies

STEPHAN TARGAN, MD:† The difficulty in infectious diarrheal syndromes is to identify which diseases require urgent versus nonemergent management. For example, in a dehydrated patient with a history of diarrhea, the decision will be whether to act immediately to reverse a potentially fatal illness, or if the disease process is self-limiting, to allow the patient to heal himself and not to intervene. With a patient who presents in shock with a history of diarrhea, the immediate fluid replacement therapy is obvious; however, knowing which patients need further rapid evaluation and further additional treatment is not always as apparent.

In order to be prepared to manage true emergencies, physicians must be familiar with both the emergent and nonemergent infectious diarrheas. The discussion will begin by focusing on how the various types of infectious diarrhea and dysentery clinically present and how one can attempt to rapidly differentiate them by: (1) obtaining appropriate historical information; (2) knowledge of presenting signs and symptoms, and (3) use of proctoscopy and studies of stool specimens. With these facts established, I will then discuss which illnesses require immediate therapy or admission to hospital (or both), the appropriate therapy and which disease entities can be managed in a less acute manner by limited diagnostic and therapeutic manipulations to the patient. An in-depth discussion of each of these diarrheal syndromes is beyond the scope of this paper.

A normal person excretes approximately 1.7

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TABLE IV-1.—*Infectious Diseases Presenting with Gastrointestinal Symptomatology*

- Diarrhea secondary to toxin production
  - Staphylococcus aureus
  - Escherichia coli (E. coli)
  - Clostridium perfringens (C. perfringens)
  - Vibrio cholerae (V. cholerae)
- Diarrhea and dysentery
  - Shigella
  - E. coli
  - Salmonella typhi (typhosa)
  - Staphylococcal enterocolitis
  - Pseudomembranous colitis secondary to antibiotic therapy
- Bloody diarrhea and dysentery
  - Entamoeba histolytica
  - Shigella
- Acute mediastinitis secondary to esophageal perforation
- Peritonitis
  - Primary (spontaneous) peritonitis
    - Nephrosis
    - Alcoholic cirrhosis
    - Tuberculosis
    - Fungal
  - Secondary peritonitis
    - Bile
    - Bacterial
      - Intraabdominal abscess
      - Gastrointestinal perforation
      - Alteration of intestinal wall permeability (i.e. intestinal obstruction, volvulus, intussusception, ischemia)

percent or between 150 to 200 ml of the 9 to 10 liters of gastrointestinal secretions produced per day. Eighty percent of this is usually absorbed by the small intestine and another 18 percent by the colon.[1] If the bowel secretes an increased amount of fluid with an increased transit time to overwhelm these very efficient mechanisms, or these absorptive mechanisms are inhibited by various agents, an increased amount of fluid is excreted and diarrhea results. There may be a pronounced variation in the electrolyte composition of the stool water which depends on the level of the gastrointestinal tract that the diarrhea develops and the rapidity of the resultant transit time. Most types of infectious diarrhea yield large amounts of sodium, chloride and bicarbonate loss or a small bowel fluid. However, when dysentery or colonic mucosal sloughing with loss of erythrocytes, leukocytes and cellular debris occurs, in addition to a small bowel diarrhea, there is also loss of protein with various additional electrolyte combinations.[1]

Diagnosis

In order to understand how to differentiate the presentations of the infectious diarrheas and dysenteries, it is helpful to have a general concept of the various pathological mechanisms. There are three basic mechanisms.[2,3]

- *Type I* is toxigenic, or an exotoxin which is produced by a replicating bacteria either in an external medium or in the intestinal milieu which causes profuse efflux of fluid and electrolytes from the small bowel.[4]
- *Type II* is superficial, longitudinally progressive colonic invasion of the mucosa by a pathogen producing both a watery diarrhea and dysentery.[5]
- *Type III* is a deep and localized penetration of both the ileal and colonic mucosas usually producing diarrhea and dysentery, but in addition systemic and toxic symptoms.[6]

Although many of the following diarrhea syndromes have classical presentations, often the patients will have history of prior diagnostic manipulation or therapy, or both, which may modify the susceptibility, presenting manifestations or severity of illness in the affected person. The following are important general questions to ask: (1) Has the patient had prior gastric surgical operation or a natural hypoacidity state? Since acid in the stomach provides a barrier to bacterial invasion, the absence of this could enable invasion and infection of the more distal gastrointestinal tract to occur with a lesser inoculum of certain pathogenic bacteria.[7-11] This could alter epidemiological histories and make them less exacting. (2) Has the patient had prior antibiotics? This type of information could provide a clue as to the cause of various syndromes which follow antibiotic use. In addition, since the products from natural intestinal bacterial flora, particularly anaerobes, act as a growth suppressant to invading pathogenic bacteria, prior therapy of antibiotics could alter the onset and duration of symptoms of certain bacterial diarrheas.[3,12-17] (3) Has the patient's rapid transit time been altered with opiates or anticholinergics, or both? Diarrhea and rapid transit time are usually protective defense mechanisms by the host to rid itself of the invading pathogen. Treatment with anticholinergic agents has been shown to exacerbate and worsen the symptoms of certain diarrheas.[2] This occurs by either enabling greater contact time between the mucosa and invading organism which increases its pathogenicity, or by the development of toxic dilation of the bowel.

Although there are tremendous overlaps between how the various infectious causes present,[2] and a spectrum of symptomatology does occur

TABLE IV-2.—*Type I: Diarrhea Secondary to Toxin Production*

Pathogen	*History*	*Presenting Clues*	*Systemic Symptoms*	*Stool Exam*
Staphylococcus aureus ...	Ingestion of foods, dairy products	Acute onset 4-8 hrs, vomiting, diarrhea (severe)	Minimal	No leukocytes
Escherichia coli	Travel	Onset 24-72 hrs, no vomiting, diarrhea (moderate)	Minimal	No leukocytes
Clostridium perfringens ..	Contaminated food, cooked meat	Onset 12-24 hrs, vomiting (±), abdominal pain (severe), diarrhea (moderate)	Minimal	No leukocytes
Vibrio cholerae	Endemic and epidemic	Onset 24-72 hrs, diarrhea (severe, "rice-water")	Hypokalemic nephropathy	No leukocytes

with each disease, some general guidelines can be made which may be useful. Since we are concerned with emergencies in this symposium, the most severe presenting manifestations will be discussed.

Type I Diarrheal Syndromes

Patients presenting with diarrhea in the absence of systemic complaints are usually suffering from one of several toxigenic types of diarrhea (Table IV-2). These are commonly of acute onset with minimal symptoms, other than general malaise usually secondary to large fluid efflux into the bowel.[3,4,18] Invariably, methylene blue staining of fresh stool specimens shows no leukocytes. Inference as to the type of toxin incriminated can be made from the history and certain presenting signs.

Staphylococcal toxin is usually produced in an external medium consisting of dairy products and baked goods, such as Boston cream pie. The incubation period is short, four to eight hours, because no bacterial growth is required in the gastrointestinal tract for toxin production. As compared with other toxins,[18] a severe amount of vomiting with an abrupt explosive diarrhea results. Escherichia coli toxin is produced in the bowel by a toxigenic strain and can be acquired as "travelers diarrhea" or endemically in "child nursery" populations. The onset is not as acute as staphylococcal disease since toxin production is dependent on proliferation within the gut. It has a fairly short incubation period of up to 48 hours.[19,20] Clostridia perfringens toxin is produced by the organism in poorly cooked meats, canned vegetables and fruits, that is, situations in which there is a lack of killing of spores. This particular toxin can produce severe abdominal pain along with a profuse diarrhea.[16,20] Vibrio cholerae is rarely isolated in this country; however, a history of endemic travel exposure and return to this country can be helpful to consider this pathogen's toxin as a possible cause of diarrhea.

Type II Diarrheal Syndromes

Patients who present with diarrhea *and* dysentery (by history or findings on tests of stool specimens) usually have some systemic symptoms, along with tremendous fluid and mucosal cell loss. On studies of stool specimens in all of these patients the presence of leukocytes will be noted. Occasionally (as discussed below), certain specific differences in the fecal leukocyte evaluation can be helpful in differentiating causes. However, the most helpful clues are differentiating historical and presenting symptomatology (Table IV-3).

Shigella can be transmitted with as few as 10 to 100 organisms.[16] A history of working with, or exposure to, personnel or patients in nursing homes where the organism is endemic is helpful to establish the person-to-person transmission of this disease. In addition, a history of recent travel to Mexico or South America should also raise the possibility of Shigella dysentery. In about 50 percent of the cases, some bloody diarrhea occurs. There is some abdominal pain; however, it is not as severe as with clostridial disease. The illness can present with progressive upper to lower gastrointestinal symptoms, such as nausea which then progresses to tenesmus, which is characteristic of the type II pathogenic mechanism. Systemic symptoms such as meningismus, seizures, upper respiratory symptoms and rhabdomyolysis do occur. Occasionally, bacteremias and septicemia with fever can occur, but are not the rule.[21]

Penetrating E. coli has no distinguishing historical characteristics. Its presentation is similar to Shigella, with findings on tests of stool also showing polymorphonuclear leukocytes.[22] These latter two entities can be only distinguished by (1) isolation of Shigella from stool culture and

(2) showing the presence of a toxigenic strain of E. coli from feces.

Salmonella dysentery, or nontyphoid Salmonella, requires 10^5 to 10^8 organisms to produce disease. The important historical clues are ingestion of egg products, poultry and the use of possibly contaminated water supplies. There is occasional bacteremia with fever, but this is the exception. On examination of stool specimens, many leukocytes are found with usually greater than 70 percent of them polymorphonuclear.[16]

Salmonella typhi or paratyphi can present initially similarly to Salmonella dysentery. The history, if positive, more classically shows there to have been endemic travel to Mexico or contact with contaminated water or food supplies. These patients can present with a multitude of systemic complaints, such as headache, cough, pharyngitis and abdominal tenderness. The patients can be in a toxic condition, with high fevers and prostration, indicative of bacteremia. Although diarrhea can be profuse, constipation can, at first, be the predominant gastrointestinal symptom. Examination of stool specimens for leukocytes can be helpful in that of all the types of dysentery, Salmonella typhi usually presents with greater than 70 percent mononuclear leukocytes. Although leukopenia and bradycardia are classically reported in typhoid, it is transient and often difficult to document.[23]

Staphylococcal enterocolitis is a true emergency where prompt diagnosis is mandatory. A history of recent antibiotic use or surgical operation, or both, is the usual predetermining factor. These patients are the ones who are most likely to present with shock with no evident prior diarrhea. Studies of stool with methylene blue or Gram stain will show many leukocytes and sheets of staphylococci. This is a specific differential point which should stimulate immediate therapy.[24,25]

Pseudomembranous enterocolitis presents following initiation of administration of antibiotics. The most common implicated have been clindamycin and lincomycin, with a few cases secondary to tetracycline and ampicillin.[26] The onset of diarrhea can occur from one day to two weeks after therapy is begun. This can present with tremendous fluid loss and toxic megacolon. Leukocytes will be shown on examination of stool and proctoscopy is necessary to differentiate this entity,

TABLE IV-3.—*Type II: Diarrhea and Dysentery*

Pathogen	*History*	*Presenting Clues*	*Systemic Symptoms*	*Stool Exam*
Shigella	Endemic; nursing home; recent travel—Mexico, South America	Bloody diarrhea (60%); abdominal pain; progressive symptoms; tenesmus	Seizures; meningismus; occasional bacteremia; fever; respiratory symptoms	Polys*; 1+ red blood cells; no organisms
Escherichia coli	Travel history	Above plus abdominal pain	Variable	Polys, ± red blood cells
Nontyphoid Salmonella	Prepared foods; poultry; egg products	"Greenish stool" or watery stool	Fever; occasional bacteremia	70% polys; 30% mononuclear cells
Salmonella typhi	Water supplies; food handling	Constipation first; headache; upper respiratory infection; "leukopenia-bradycardia"	Elevated temperature (spiking); toxic symptoms	70% mononuclear cells; 30% polys
Staphylococcus aureus (enterocolitis)	Prior antibiotics	Severe dehydration leading to shock	Comatose	Sheets of staphylococci + leukocytes
Pseudomembranous (enterocolitis)	Clindamycin; other antibiotics	Classic ulcers on proctoscopy	Minimal	+ leukocytes

*Polymorphonuclear cells

TABLE IV-4.—*Type III: Bloody Diarrhea*

Pathogen	*History*	*Presenting Clues*	*Systemic Symptoms*	*Stool Exam*
Entamoeba histolytica	Mideast; Mexico	Few abdominal signs; toxemia; peritonitis; 20-30 bowel movements/day (can be *watery*); tenesmus; *ulcers* on proctoscopy; abdominal mass	Malaise	+ leukocytes; + wet mount; + Schaudin's prep
Shigella	USA; travel	Prolonged course (>5-7 days)	Malaise	+leukocytes
Shiga bacillus	Rare in the USA; travel	Toxic; fluid loss	Dehydration	Leukocytes; red blood cells

having classical pseudomembranes on the mucosa, from other modified dysenteries, or particularly staphylococcal enterocolitis.[26,27]

Type III Diarrheal Syndromes

In patients who present with predominantly bloody diarrhea, and appear either acutely ill or in a toxic condition, usually there is one of two infectious causes (Table IV-4). The presentation and severity of amoebic colitis is quite variable, but what will be described here is the most severe type. These patients can present with chronic diarrhea with an acute exacerbation, or the initial symptomatology may be the rapid onset of watery diarrhea. A travel history to Mexico or the Middle East, if positive, can be helpful. Usually the patient has some tenesmus and can have peritoneal signs or abdominal mass, or both. On examination of stool, motile amoeba on heated wet mount may be shown, but proctoscopy with several Schaudin's preparations is a must. A diagnosis is made by seeing the ulcerations on colonic examination with the presence of amoeba shown on a smear.[28]

Shigellosis, particularly with the Shiga bacillus (Shigella dysenteriae) as the etiologic agent, can have a prolonged course and patients may be in a toxic condition and have bloody diarrhea. Recent travel history to endemic areas, such as India and Pakistan or Mexico, should be elicited from patients. Generally, the conditions of these patients are not as toxic as in patients with amoebic disease. Study of stool specimens might be helpful in differentiating these two diseases if there is a lack of amoeba seen. However, culture gives the definitive diagnostic clue.

If none of the above is revealing, other more chronic forms of noninfectious bloody diarrheas —such as ulcerative colitis, ischemic colitis or vasculitis—should be considered as diagnostic possibilities. As a helpful review, Tables IV-5 and IV-6 list the major historical data and certain presenting signs and symptoms most commonly associated with specific etiological agents causing diarrhea.

TABLE IV-5.—*Major Historical Data*

Major Historical Point	*Pathogen*
Travel	Escherichia coli Entamoeba histolytica Vibrio cholerae Shigella
Antibiotics	Staphylococcal enterocolitis; pseudomembranous
Dairy products; baked goods	Salmonella (nontyphoid) Staphylococcal toxin
Water supplies "closed"	Salmonella typhosa
Meat and canned goods	Clostridium perfringens

TABLE IV-6.—*Major Presenting Symptom or Sign*

Major Sign or Symptom	*Pathogen*
Vomiting	Staphylococcus aureus (toxin); Salmonella
Shock (alone) with diarrhea	Staphylococcus aureus (enterocolitis)
Elevated temperature	Salmonella typhi Entamoeba histolytica Shigella
Abdominal pain (general)	Entamoeba histolytica Clostridium perfringens Escherichia coli (toxin)
Tenesmus	Escherichia coli (penetrating); Shigella; Entamoeba histolytica
Systemic-toxic	Salmonella typhi Entamoeba histolytica (colitis)
"Appendicitis"	Salmonella typhi

Therapy

A useful therapeutic approach is to be aware of the mode of presentation and natural course of the various types of diarrhea. This will aid in instituting necessary treatment and conversely, avoiding unnecessary therapeutic approaches. Table IV-7 lists the modes of presentations with their most likely etiologic agents. The clinical presentations can be characterized as follows:

- Acute and fulminant onset with progressive course, sometimes rapid.
- Acute and often fulminant presentation, with a self-limited course.
- Chronic mode of presentation with an acute exacerbation and often fulminant course.

Using these groups as guidelines for therapy, a review of therapeutic maneuvers with prognostic evaluation will be discussed. The first group of diseases with rapid onset are usually rapidly progressive and there should be immediate admission to hospital or intervention, or both, for patients affected (Group A, Table IV-7).

When the diagnosis of toxic amoebic colitis is made from the criteria stated above there should be immediate admission to hospital with fluid replacement and therapy with antiamoebic drugs should be started. Those drugs should be either

TABLE IV-7.—*Clinical Course and Most Common Cause in Diarrheal-Dehydration Syndromes*

Group A: Acute fulminating and rapidly progressive
Amoebic colitis
Staphylococcal enterocolitis
Vibrio cholerae
"Pseudomembranous enterocolitis"
Group B: Acute fulminating and self-limited
Toxic—staphylococcal
Escherichia coli (toxigenic)
Clostridium perfringens
"Shigella" toxin
Salmonella dysentery
Shigella dysentery
Escherichia coli
Group C: Chronic-acute exacerbation fulminant
Amoebic colitis
Salmonella typhi

metronidazole (750 mg given orally three times a day for 10 to 14 days) or combinations of emetine (1 mg per kg of body weight given intramuscularly), chloroquine (250 mg given four times per day for 2 days, then twice a day for 12 days) and diiodohydroxyquin (650 mg given three times a day for 21 days). If peritoneal signs, some hypotension, fever and a toxic condition are present, a physician should only wait 12 to 24 hours to see if there is improvement with supportive and chemotherapeutic approaches before deciding whether to intervene surgically. There is a high mortality from perforation and toxic megacolon with the severe form of this disease entity and, therefore, use of anticholinergics is to be avoided. The prognosis, even with surgical intervention, is very poor.[28]

Once staphylococcal enterocolitis is diagnosed from findings on studies of stool specimens, blood cultures should be made, a central venous line should be inserted and vigorous fluid replacement begun to maintain adequate circulating volume. Chemotherapy with vancomycin, 2 grams given orally per day (these are usually penicillin-resistant staphylococci) and 2 grams given intravenously, should be begun.[29] The fluid loss may be enormous and may last several days to weeks. However, clinical response can occur much earlier in the course with rapid appropriate therapy. The prognosis is poor, but it is extremely important to persist with therapy.[24,25,29]

After proctoscopic evaluation and diagnosis of pseudomembranous enterocolitis, the insighting agent should be discontinued immediately. The patient is admitted to hospital to correct any dehydration, and closely observed for any signs of toxic megacolon or perforations. Anticholinergics, such as diphenoxylate hydrochloride with atropine sulfate (Lomotil®), must be avoided as they can increase the possibility of these complications. Reversibility of diarrhea should be expected to occur between two and five days after discontinuation of therapy with antibiotics.[26,27] The prognosis is good if the disease is diagnosed early. However, up to a 26 percent mortality from this disease has been reported and therefore the importance of early recognition must be stressed.[27]

Although it is rare, when diarrhea due to Vibrio cholerae is diagnosed, the patient should be admitted to hospital and treated with either orally given electrolyte solutions containing glucose or intravenously given electrolyte fluids. Since there is usually only an increased efflux of fluids and electrolytes produced by the toxin, and the absorptive mechanism remains intact in the small bowel, oral treatment is possible.[4,11,20] In addition, orally administered tetracycline decreases the duration and severity of the illness. Future therapy may include using antiprostaglandin compound, indomethacin. There is evidence suggesting that prostaglandins might be an intermediary agent that increases the stimulation of adenylcyclase production by this toxin.[20] Stimulation of adenylcyclase increases the efflux of fluid from the bowel.

Those entities that can present acutely and similarly to the above illnesses, but are self-limited (Group B, Table IV-7), usually do not require that the patient be admitted to hospital and demand restraint from the physician as to vigorous therapy.

Toxic types of diarrhea are self-limited and commonly require only oral fluid support. The course can be up to a maximum of 36 hours before resolution. Any persistence of diarrhea beyond that time requires reevaluation as to an alternative cause. Occasionally admission to hospital is required for fluid replacement. Short courses of anticholinergics can help relieve symptoms without exacerbating the course.[4,11,16,18]

When the diagnosis of dysentery due to Salmonella is made, no therapy is usually needed. Fluid support and reassurance is most helpful. Antibiotic therapy is generally not indicated (unless patients appear septic or are bacteremic) since it may potentiate carrier states and possibly prolong the illness.[17,30] Diarrhea generally lasts three to five days and reevaluation is indicated if symptoms persist beyond this point. Brief courses of anticholinergics have been used but they should

be avoided so as to minimize prolongation of illness.[16]

Shigellosis that patients acquire in the United States or Mexico has an acute onset, but is generally a self-limited disease. Admission to hospital is usually not required, although with persistent diarrhea, dehydration and toxic symptoms, this occasionally becomes necessary. Fluid support is the most important treatment method. Home enteric isolation should be instituted because of the extremely small inoculum required for transmission of the disease. Use of anticholinergics is to be avoided at all times because they increase the symptoms and duration of illness.[16] If admission to hospital is required, ampicillin or tetracycline therapy is suggested. Antibiotic treatment also should be considered for outpatients if diarrhea persists beyond the usual five days.[21]

At times, certain diarrheal syndromes will present with a long indolent, benign course with a superimposed acute exacerbation, which requires therapeutic intervention (Group C, Table IV-7). For example, in a patient infested with amoeba there can be a chronic period of mild symptoms, then the condition can acutely exacerbate and the patient present to the physician with the identical clinical features as in those persons with the primary acute disease. The same diagnostic and therapeutic guidelines are still relevant and apply to these patients.

Salmonella typhosa is another pathogen causing infectious diarrhea that can have a chronic course with undulating fevers and symptoms. A patient with this prior history may present with toxic symptoms, severe diarrhea and dysentery. After making the diagnosis from results of appropriate cultures (blood, urine, stool or bone marrow), the patient should be admitted to hospital, treated with fluids and antibiotics and observed for possible small bowel perforation.[16] The antibiotics of choice are parenterally given chloramphenicol or ampicillin continued until patients are afebrile for at least five to seven days. Because an increasing number of isolates from Mexico are resistant to chloramphenicol, patients from this geographic area should be treated initially with ampicillin.[31] Generally, some clinical response will be observed within five days; however, if symptoms persist, the possibility of antibiotic resistance must be considered and confirmed by *in vitro* susceptibility studies. Besides chloramphenicol and ampicillin, trimethoprim-sulfamethoxazole is another effective agent against most strains of S. typhosa and can be used as an alternative drug. Additionally, persistence of symptoms may be secondary to peripheral focal disease, such as sequestered abscess, osteomyelitis or cholecystitis. A careful and extensive evaluation for these potential sources of persistent bacteremia must be instituted.

Acute Mediastinitis

NORMAN PANITCH, MD:* Perhaps in the 1970's it is appropriate for a clinical gastroenterologist to discuss the syndrome of acute mediastinitis. Acute mediastinitis was at one time a prevalent disorder. Before the advent of modern culture techniques and potent antibiotics, bacterial infections within the neck, lung, pleura and vertebrae would tend to spread along available fascial planes and invade the mediastinum. In the 1970's, because of the easy availability of upper gastrointestinal endoscopy, esophageal dilatation and high speed ballistics, acute mediastinitis is almost always secondary to some condition that has resulted in esophageal perforation.

Anatomic and Bacteriologic Considerations

The mediastinum is a potential extrapleural space which communicates with other potential spaces of the chest and neck. Infections involving the pretracheal space arise from perforations of the anterior wall of the esophagus as well as from the spread of infections from the lateral pharyngeal spaces and the pyriform fossae. The above infections may then spread into the mediastinum. Posterior perforations of the cervical esophagus involve the retrovisceral space. The latter is the most common mode of spread of infection into the mediastinum since most perforations in the cervical esophagus traverse the posterior wall. The upper two thirds of the thoracic esophagus lie to the right of the midline and, consequently, perforations here would tend to lead to right pleural effusions, whereas the lower third of the thoracic esophagus curves gently to the left of the midline. Perforations of the distal esophagus, therefore, lead to associated left pleural involvement. Respiratory dynamics appear to influence the spread of inflammation into the mediastinum. Negative intrathoracic pressure will tend to attract irritative oral and gastric contents into the mediastinum resulting in chemical mediastinitis. The esophagus, like the rest of the upper gastrointestinal tract, derives its microflora from the mouth.

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TABLE IV-8.—*Acute Mediastinitis—Etiologic Factors*

Esophageal Perforation
Instrumental
Noninstrumental
Postemetic
Foreign body
External trauma
Neoplasm
Caustic ingestion
Infections of Adjacent Structures
Lung and pleura
Subphrenic extension
Osteomyelitis

The microflora of the esophagus is scanty, a mixture of aerobic and anaerobic organisms and as a rule is penicillin sensitive.

Etiologic Factors[32] (see Table IV-8)

Perforations of the esophagus are infrequent but catastrophic when they occur.[33] They can occur secondary to *external trauma* such as gunshot wounds and stabbings, or may be seen following *internal trauma,* as with sharp foreign bodies, caustic ingestions and instrumentation, or may occur spontaneously. The diagnosis is usually suspected after a brief history or physical examination. The latter shows supraclavicular or subcutaneous crepitations. Pleural effusions can develop if the thoracic or distal esophagus has been perforated. On x-ray films of the chest, pneumomediastinum, pneumothorax, hydropneumothorax or subcutaneous emphysema may be seen. An esophagram using a water soluble medium is frequently helpful in delineating the site of perforation. If the latter is negative, and the diagnosis is strongly suspected, esophagoscopy with minimal air insufflation is then recommended.

Perforation due to instrumentation. As the field of internal medicine becomes increasingly more "invasive," perforation of the esophagus secondary to instrumentation has become more prevalent. By instrumentation I mean diagnostic endoscopy, bougienage for esophageal strictures, pneumatic dilatation for achalasia and diffuse esophageal spasm and the placement of Linton and Sengstaken-Blakemore tubes in the treatment of bleeding varices. It should be noted that with flexible fiberoptic endoscopes and proper supervision, this complication has become rare at large university hospitals. At Harbor General Hospital in almost a two-year period in which about 1,000 upper gastrointestinal endoscopies have been done, there has not been a single esophageal perforation secondary to esophagoscopy.

At the time of instrument perforation, most patients will complain of immediate retrosternal pain and dysphagia. The onset of fever, leukocytosis and dyspnea heralds true mediastinitis. Once perforation has been shown to have occurred, surgical consultation should be immediately obtained. Antibiotics in high doses should be used whether or not immediate surgical operation is advised. Penicillin administered intravenously is the drug of choice. In most patients emergency surgical procedures will be required for primary repair of the perforation. Two layered closures of the esophagus are recommended along with drainage of the mediastinum. An occasional patient can be treated with local cervical drainage if the suppuration has become chronic or localized, or both.

Postemetic perforation.[34] The syndrome of spontaneous rupture of the esophagus deserves special note for it is diagnosed antemortem in only about half the cases. The first clear description of this entity was published in 1724 by Herman Boerhaave, a physician practicing in Holland. The patient, Johannes, Baron of Wassenaar, a 51-year-old admiral of the Republic and Dikereene of the Rhineland became critically ill after gorging himself on a duckling dinner and inducing emesis, which he frequently did after his debauchery. He complained of a tearing in his chest with the sudden onset of chest and back pain. He died hours later. Dr. Boerhaave, who did the autopsy, placed a needle in the left side of the patient's chest and noted the aroma of duckling. He quickly deduced that the Admiral had ruptured his esophagus.

In current series describing this entity it should be noted that in about 5 percent of patients there is no pain and in about 20 percent an x-ray film of the chest shows no abnormalities. The classic x-ray findings observed in this condition include a pneumomediastinum and a left pleural effusion. The former can sometimes be seen as a linear lucency outlining the border on the left side of the heart. The pleural effusion has a high amylase content derived from the salivary isoenzyme. Immediate use of barium or preferably maglumine diatrizoate (Gastrografin®) swallow is indicated, followed by esophagoscopy if the contrast study is negative. Once the diagnosis is confirmed, high dose penicillin therapy is instituted, hypotension is corrected with volume repletion and the patient is then taken to the operating room where a two-layered closure is carried out. Most surgeons

TABLE IV-9.—*Intestinal Microflora*

Proximal Small Intestine
Aerobes (Streptococcus, Lactobacillus, Candida)
$<10^5$/gm
Distal Small Intestine(transition zone)
Aerobes, Anaerobes
10^5-10^7/gm
Colon
Anaerobes (Bacteroides, Bifidobacterium, Peptostreptococcus); Aerobes (Escherichia coli)
10^7-10^{11}/gm

recommended a fundic patch to buttress the weakened area.

Peritonitis

The peritoneum is a serous surface with an area of about 50 percent of the external body surface. It is easy to appreciate that inflammation of a large portion of the peritoneum would result in massive fluid shifts within the abdomen. Within 24 hours, the volume within the abdomen may reach 5 to 10 liters. Inflammation also permits absorption of toxic and metabolic products. Inflammation of the peritoneum produces immediate effects upon intestinal function. Paralytic ileus and distention soon are observed. The above changes have their ultimate effects upon the cardiopulmonary system with resulting shock, respiratory and myocardial depression.

The symptoms and signs of peritonitis may be divided into two phases, *reflex* and *toxic*.[35] The reflex symptoms and signs are early and include pain, vomiting, an anxious facial expression and superficial hyperesthesia. Later, the toxic signs of abdominal distention, ileus and toxemia appear. The latter are more serious. Alterations in temperature and clinical shock may be either reflex or toxic.

In order to appreciate the bacteriology involved in peritonitis from any of the innumerable causes, we will at this point briefly review the general microflora of the gastrointestinal tract (Table IV-9). In order to initiate empirical, early antibiotic therapy before cultures are available, it is important to realize that the bowel microflora differs quantitatively and qualitatively depending upon basic anatomic location.[36] Under normal conditions, the upper small intestine has a relatively sparse, endogenous aerobic bacterial flora. The predominant organisms in the duodenum, jejunum and proximal ileum are the streptococci, Lactobacillus and the fungus, Candida albicans, at less than 10^5 organisms per gram. Significant growth of up to 10^7 organisms occurs only in the distal ileum where anaerobic bacteria begin to become numerically important. As one crosses the ileocecal valve, the flora changes dramatically. In the colon, the anaerobes predominate—that is, Bacteroides, Bifidobacterium, Peptostreptococcus and Clostridium. Anaerobes in the colon outnumber the coliforms 1,000-10,000:1. This takes on clinical importance when one considers injury to the bowel in a normal person. Colonic injuries have a rather high incidence of secondary anaerobic infection. As a rule of thumb, perforation or rupture of the large bowel must be treated with antibiotics which cover both aerobes and anaerobes, such as gentamicin and clindamycin hydrochloride, while upper intestinal injuries can be treated with penicillin alone. Chloramphenicol still remains an excellent drug in treating anaerobic infections and is an effective alternative to clindamycin. Tetracycline has been relegated to a second-line status for treating anaerobes because of the identification of resistant strains of Peptostreptococcus and Bacteroides.

Classification of Peritonitis

Peritonitis can be simply classified as being either primary or secondary. Primary peritonitis is generally due to an infectious process with bacteria being the most common pathogen. Secondary peritonitis is usually related to perforation with infection then predominating. A good rule to remember is that primary bacterial peritonitis is almost invariably *unimicrobial,* whereas secondary bacterial peritonitis (peritonitis which follows or complicates another disease or injury of the abdomenal contents) is invariably *polymicrobial.* In addition, the secondary form is characterized by bacterial flora of anaerobic predominance, whereas anaerobes are rarely, if ever, involved in primary peritonitis.

Primary or Spontaneous Peritonitis

Primary Bacterial Peritonitis of Nephrosis

The first type of primary peritonitis that we will consider is that of pneumococcal peritonitis. This disorder has become a rare disease. It is a disease of children, usually seen in young girls with nephrotic syndrome. Associated pulmonary infections are not usually noted. It is characterized by the sudden onset of fever, abdominal distention and tenderness. Vaginal smears and cultures show the presence of the pneumococcus in a mi-

TABLE IV-10.—*Spontaneous Bacterial Peritonitis of Cirrhosis*

Setting
Decompensated cirrhosis
Ascites
Portal hypertension
Signs
Fever—81 percent
"Peritoneal signs"—65 percent
Bowel sounds decreased or absent—64 percent
Hypotension—69 percent
Laboratory
Leukocytosis—72 percent
Positive blood cultures—76 percent
Abnormal liver function tests
Characteristic ascitic fluid
Ascitic Fluid
"Infected transudate" (protein <2.5 gm per 100 ml) >250 cells per cu mm (polymorphonuclear cells)
Positive identification on Gram stain—40 percent
Single organism isolated (Escherichia coli, Pneumococci, Klebsiella, Enterococci)
Anaerobes not implicated

nority of cases. The peritoneum is found to be covered by a greenish watery exudate if laparotomy is undertaken for diagnosis. The treatment of choice is parenterally given penicillin for at least one week.

Streptococcal peritonitis, usually caused by the β-hemolytic streptococci, is also an uncommonly observed disease in the antibiotic era. It is seen in the above clinical setting and treated in a similar manner.

Spontaneous Bacterial Peritonitis of Cirrhosis (SPC)

SPC has become a relatively common entity. It has a reported prevalence of 3 percent in cirrhosis and 8 percent in cirrhotic ascites. The clinical situation is one of decompensated liver disease, usually cirrhosis, associated with the classic signs of portal hypertension including splenomegaly, esophageal varices and ascites. The latter is considered the sine qua non of the disease. Clinically, most patients have fever, abdominal pain, "peritoneal signs," impending hepatic coma and decreased or absent bowel sounds see Table (IV-10).

Laboratory findings include peripheral leukocytosis, abnormal values on liver function tests, positive blood cultures with the same organism as that found in the ascitic fluid (76 percent) and characteristic ascitic fluid changes. The ascitic fluid has the character of an "infected transudate." It is extremely rare to find the protein content of the ascitic fluid greater than 2.5 grams per 100 ml. This brings us to the question of what is "normal" ascites in regard to total cell count and differential count. Most authors have considered a total leukocyte count of less than 300 per cu mm and a polymorphonuclear (PMN) percentage of under 25 normal. Using these data, more than 90 percent of patients in a large series of patients with spontaneous peritonitis had an increased total leukocyte count (>300) and all had an increase in the PMN percentage in the ascitic fluid (>25 percent).[37]

The most commonly noted organisms cultured from infected ascites are E. coli followed by the pneumococcus, Klebsiella, enterococcus, streptococcus and Pseudomonas. It is extremely rare to find multiple or anaerobic organisms. Gram stain of the ascites is positive in about half the infected patients.

Regarding treatment, an immediate diagnostic paracentesis in all patients with ascites should be done. If the total leukocyte count is greater than 300 cells per cu mm or the percentage of PMN's is greater than 25 percent in an unstable patient with cirrhotic ascites, empirical antibiotic therapy appears to be indicated with penicillin and gentamicin pending the culture report. If more than one organism is isolated, a diagnostic search for a potential source of sepsis is indicated, such as diverticulitis with perforation. The same diagnostic evaluation is indicated if anaerobes are grown from the ascitic fluid, for as mentioned above, anaerobes do not appear to be associated with spontaneous peritonitis in patients with cirrhosis with any great frequency. Prognosis for this disease appears to be improving. In a 1971 report[37] only 3 percent of patients with SPC left the hospital while in a 1974 review[38] 20 percent were discharged, although the peritonitis was in fact arrested in about 60 percent in both series. This stresses the fact that these patients are extremely ill in addition to the peritonitis.

Tuberculous Peritonitis[39,40]

This is an unusual form of tuberculosis (Tbc), yet it is extremely important to identify. Most cases are due to reactivation of latent Tbc in the peritoneum established earlier at the time of hematogenous spread from a primary, usually pulmonary focus. Most patients with Tbc peritonitis do not have concurrent, active pulmonary, intestinal or genital Tbc. It is a disease usually seen in large municipal hospitals with their populations of pa-

tients with cirrhosis and poorly nourished and debilitated patients.

Clinically, Tbc peritonitis is an insidious disease presenting with fever, anorexia, weakness and weight loss. Ascites is found in almost all patients upon physical examination and more than half of the patients have complaint of abdominal pain which is usually diffuse in nature. The classically described "doughy" abdomen is rare. Intermediate purified protein derivative (PPD) skin test is virtually always positive if the process is not part of miliary Tbc. If miliary Tbc is present, 20 percent of patients will be anergic but a PPD test will be positive with successful therapy. An x-ray film of the chest may or may not be helpful.

The organism has been retrieved from the ascitic fluid about 80 percent of the time when more than 1 liter of ascitic fluid was cultured.[39] Results are poor when small amounts are cultured.[40] Blind peritoneal biopsy is positive in two thirds of cases and peritoneoscopy, with direct biopsy of the peritoneum, is strongly recommended when the diagnosis is suspected. The ascitic fluid characteristics ("Rule of 25's") which should make one consider Tbc peritonitis are the following: protein, greater than 2.5 grams per 100 ml; cells, greater than 250 cells per cu mm; lymphocytes, greater or equal to 75 percent (PMN's less than 25 percent).

Most authorities recommend triple therapy with isoniazid, ethambutol and streptomycin for three months, then discontinuing administration of streptomycin and continuing to give the other drugs for an additional 15 months. If the process was extremely indolent and long-standing before initiating therapy, corticosteroids may be added initially for three months and then tapered for six weeks and discontinued. The addition of corticosteroids is recommended by some authorities to prevent the development of adhesions at a later time with resulting intestinal obstruction and volvulus.

Fungal Peritonitis

Systemic candidiasis and histoplasmosis have been rarely reported to cause massive ascites and peritonitis by direct peritoneal involvement. This condition should be considered in the appropriate clinical setting, such as parenteral hyperalimentation or infected prosthetic heart valves.

Secondary Peritonitis

Bile Peritonitis

This condition usually arises after biliary surgical operation although traumatic, inflammatory and spontaneous perforations have been reported within the biliary tract. The diagnosis should be suspected in the appropriate clinical setting along with the suggestive chemical findings of a high conjugated bilirubin with a normal alkaline phosphatase determination.[41]

Bacterial Peritonitis

This condition results from a complication of a primary, usually serious, disease or injury of the abdominal cavity or its contents. The resulting peritonitis usually follows a perforation of the alimentary or genitourinary tract and is invariably polymicrobial with anaerobic organisms often predominating. The aerobic organisms commonly found include E. coli, Enterobacter, Streptococcus, Klebsiella, Pseudomonas, Proteus, Staphylococcus, Candida and diphtheroids. The anaerobic organisms include Bacteroides, Peptostreptococcus and Clostridium.

The aerobes and anaerobes seem to be synergistic in their pathogenic effect. Virulence appears to be greatly enhanced by the presence of devitalized tissue, blood products, irritants, foreign bodies and gastrointestinal enzymes.

Peritonitis secondary to biliary, gastroduodenal and activated pancreatic secretions is due to chemical irritation and inflammation for the first 12 to 24 hours, then subsequent bacterial invasion is responsible for the inflammatory process. Colonic injury with peritonitis was formerly considered to be more serious than upper gastrointestinal perforation because of the inability to control the anaerobes which reside in the large bowel, but at present small intestinal injury has a higher mortality rate because of the high concentration of gastrointestinal enzymes released into the abdominal cavity with resultant, aforementioned chemical inflammatory process of the peritoneum.

The topics of secondary peritonitis and intraabdominal abscesses are intimately related.[42] Table IV-11 lists, in approximate order of occurrence, the sources of intraabdominal abscesses. The discussion will be directed toward only the most prevalent conditions.

Peritonitis and abscess formation secondary to appendicitis.[43] Obstruction and infection are the

TABLE IV-11.—*Intraabdominal Abscesses—Source*

Appendicitis
Pancreatitis
Genitourinary
Biliary
Diverticulitis
Perforated ulcer (peptic vs. infectious)
Inflammatory bowel (granulomatous, ulcerative colitis)
Ischemic bowel
Osteomyelitis
Amebiasis, Actinomycosis

two factors which are most important in the pathogenesis of human appendicitis. Obstruction leads to an increase in intraluminal pressure producing interference with venous outflow which results in thrombosis, hemorrhage, edema and bacterial invasion of the wall of the appendix.

The classic clinical sequence of events seen in acute appendicitis are upper abdominal pain migrating to the right lower quadrant (which is seen in only half of patients), followed by anorexia, nausea and vomiting, and then fever. In only 10 percent of patients are appendoliths seen on plain films of the abdomen. Positive findings on an abdominal film combined with an appropriate history and physical virtually assures the diagnosis. Other x-ray findings are a sentinel loop in the right lower quadrant, obliteration of the right psoas shadow, gas bubbles in the right lower quadrant (with perforation) and gas in the appendix. The latter is rarely noted in normal persons.

Peritonitis is found in a third of all cases at surgical operation but in patients over 60 years old this figure rises to 70 percent. Perforation with peritonitis is suspected when there is increasing abdominal tenderness over a widening area with high fever and leukocytosis. Late findings include abdominal distention and vascular collapse. The infection is polymicrobial and usually three to seven organisms are isolated. For stable patients with the findings of a local right lower quadrant abscess or a clinical history of a perforated appendix five or more days previously, management consists of nasogastric suction, therapy with antibiotics (gentamicin and clindamycin), correction of fluid and electrolyte disorders, and bedrest. A well localized abscess can be drained extraperitoneally, such as through the rectum. After the inflammation has subsided, the appendix should be removed at the earliest possible time. When surgical operation is done, aspiration of pus and drainage of appropriate areas of the abdomen are carried out—that is, cul-de-sac, right paracolic gutter and the involved area of the caecum. Peritoneal lavage with antibiotics is not recommended because of peritoneal irritation and dissemination, and moreover preoperative use of antibiotics makes lavage unnecessary.

Diverticulitis with perforation.[44] Diverticulitis by our definition means perforation of a diverticulum, not only an inflammation within a diverticulum. Perforation may be generalized or local with abscess formation. The abscess may surround the colon and cause obstruction, or the abscess may burrow into adjacent organs—uterus, vagina, small intestine, bladder or abdominal wall—and may, therefore, mimic Crohn's disease of the colon. The typical attack of diverticulitis is characterized by left lower quadrant pain, chills, fever and peritoneal signs. A tender mass over the sigmoid may be palpated. (It should be noted that left lower quadrant pain and a mass in this area may be secondary to diverticulosis with pronounced muscular hypertrophy.) One should make the diagnosis of diverticulitis when fever, chills and leukocytosis are associated with the above physical findings. Findings on analysis of urine may be abnormal due to contiguous involvement of the bladder or left ureter by a pericolic abscess.

Proctoscopic examination may be done to exclude other disorders (for instance, Crohn's disease) but should be done without preparation and without air insufflation. A limited barium enema using anticholinergics with a water soluble material may be done if the diagnosis is in doubt. A word of caution: do not use morphine or codeine for analgesia. Both drugs can dramatically raise the pressure within the involved colon. Meperidine does not share this property with morphine.

Therapy may be medical in a patient who is unsuited for immediate surgical operation, or for a patient in whom this is the first episode of diverticulitis and there is dramatic response to nonoperative therapy. If clinical deterioration occurs or if the mass appears to be enlarged while being treated medically, immediate surgical intervention is indicated. Surgical operation for diverticulitis with perforation should be a three-staged procedure:

- Drain abscess, close perforation and carry out proximal colostomy.
- Resect involved area with end to end anastomosis.
- Close colostomy.

If a definitive resection is attempted initially in an area of suppuration, great morbidity will be seen—such as fistulae or anastomotic breakdown.

Gastroduodenal perforations. Approximately 5 percent of peptic ulcers perforate at some time. The ratio of duodenal to gastric ulcers that perforate is 15:1, whereas the ratio of duodenal to gastric ulcers in incidence is 5:1. Most are free perforations into the peritoneal cavity. The initial presentation is that of a dramatic chemical peritonitis with the patient having a board-like abdomen and early shock. Hours later a deceptive improvement occurs in many patients as a result of dilution and neutralization of gastroduodenal contents. This is followed by signs of general, now bacterial, peritonitis. The mortality rate for untreated perforated peptic ulcer doubles after eight hours, emphasizing the need for early diagnosis and treatment.

Treatment in most instances is immediate surgical operation. Exceptions to this rule include those patients in whom the perforation is rapidly sealed off by omentum or viscera. In this case, nasogastric suction for two to three days and administration of fluids and antibiotics may be tried. Any suggestion of increasing peritoneal signs or clinical deterioration should prompt immediate surgical procedures. The second possibility for nonoperative therapy of a free ulcer perforation may be made in the management of patients with another grave illness which would significantly increase surgical mortality, such as myocardial infarction or respiratory failure. Most surgeons now favor doing a definitive acid-lowering procedure during the emergency operation. In two thirds of patients treated by simple closure additional definitive surgical procedures for ulcer will be needed within five years. Definitive acid-lowering procedures currently recommended are either vagotomy and drainage or vagotomy and antrectomy with closure of the perforation.

Pancreatitis with abscess.[45] Acute pancreatitis with the initial chemical peritonitis secondary to the release of pancreatic enzymes is a familiar clinical entity. In 4 percent of patients with acute pancreatitis a secondary pancreatic abscess develops. Untreated pancreatic abscesses are almost uniformly fatal. Bacteria are cultured from over 90 percent of these abscesses. This complication usually occurs one to four weeks after initial improvement in a patient with pancreatitis. The origin of bacterial contamination of the pancreas is unknown but is most likely due to direct transmural penetration from the transverse colon which is usually involved concomitantly with the acute pancreatic inflammatory process. The abscess may spread from the lesser sac to the subphrenic spaces (left or right) or even rarely dissect into the mediastinum, transverse colon, sigmoid, psoas or scrotum.

For diagnosis, unfortunately, amylase elevations are inconsistent and blood cultures may or may not be positive. Usually an upper gastrointestinal series or barium enema (or both) is needed to define a retrogastric mass. Abdominal sonography has become a useful diagnostic approach in evaluating pancreatic pseudocysts and abscesses. Therapy for this disease entity has been somewhat disappointing.

Although spontaneous drainage of the abscess into an adjacent viscus does occur, it is inadequate therapy. However, even with adequate prompt surgical drainage of the abscess, there is a 33 percent mortality rate. It should be noted that use of prophylactic antibiotics during pancreatitis does not prevent the subsequent occurrence of an abscess and may even lead to the selection of resistant organisms.

Typhoid ulceration and peritonitis. Typhoid fever may be complicated by peritonitis. Involved Peyer's patches may undergo necrosis and ulceration with perforation. Sudden development of severe localized pain in the right lower quadrant in a patient with typhoid during the second or third week of illness suggests the diagnosis. If leukopenia is present, it may convert to a sudden pronounced leukocytosis. Rapid surgical intervention is indicated with resection of the involved bowel under proper antibiotic coverage.

Tuberculous ulcers with bacterial peritonitis. Tuberculosis (Tbc) of the intestine is at times clinically and radiologically indistinguishable from Crohn's disease. Rarely, free perforation may complicate Tbc of the terminal ileum and caecum. Treatment would include immediate segmental resection along with anti-Tbc therapy and antibiotics for the resulting bacterial peritonitis.

Ulcerative, granulomatous and amoebic colitis. Toxic megacolon occurring in a patient with the above conditions carries a high mortality and is usually associated with multiple microperforations of the colon. The resulting peritonitis is bacterial in cause.

Nonperforated lesions of the gastrointestinal tract associated with peritonitis. Intestinal obstruction, volvulus, intussusception and ichemia

of either the small intestine or colon will result in increased permeability of the bowel wall with subsequent peritonitis. Surgical treatment of the underlying process is essential in order to contain the subsequent peritonitis.

TRADE AND GENERIC NAMES OF DRUGS

Cleocin® ..... *clindamycin HCl*
Lincocin® ..... *lincomycin*
Achromycin®, Panmycin®,
Tetracyn® .... *tetracycline HCl*
Polycillin®, Omnipen®, Totacillin®,
Amcil®, Penbritin®, Principen® ..... *ampicillin*
Flagyl® ..... *metronidazole*
Emetine HCl ..... *emetine HCl*
Aralen® phosphate ..... *chloroquine phosphate*
Diiodohydroxyquin ..... *diiodohydroxyquin*
Chloromycetin® ..... *chloramphenicol*
Bactrim®, Septra® .... *trimethoprim-sulfamethoxazole*
Lomotil® .... *diphenoxylate HCL with atropine sulfate*
Gastrografin® ..... *meglumine diatrizoate*
Penicillin G ..... *penicillin G*
Garamycin® ..... *gentamicin*
INH®, Triniod®, Nydazid® ..... *isoniazid*
Myambutol® ..... *ethambutol*
Streptomycin ..... *streptomycin*
Morphine ..... *morphine*
Codeine phosphate ..... *codeine phosphate*
Demerol®, Mepergan® ..... *meperidine HCl*
Vancocin® ..... *vancomycin*
Indocin® ..... *indomethacin*

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Newer Aspects of Some Interesting Lipid Storage Diseases: Tay-Sachs and Gaucher's Diseases

Seventh Annual Paul M. Aggeler Memorial Lecture

Delivered October 5, 1976, San Francisco General Hospital Medical Center

ERNEST BEUTLER, MD, *Duarte, California*

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Associate Professor of Medicine, and H. David Watts, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, CA 94143.

DR. WALLERSTEIN:* Dr. Beutler had his formal education at the University of Chicago where he earned his MD degree in 1950. He went through residency and fellowship there and stayed on the staff until 1959 when he assumed directorship of the Division of Medicine at the City of Hope. He is also Clinical Professor of Medicine at the University of Southern California. The most outstanding of his many prestigious lectureships is perhaps the Stratton Lecture at the American Society of Hematology in 1974.

He is a member of the Central, the Western and the American Societies of Clinical Investigation, the Association of American Physicians, and the National Academy of Sciences.

His bibliography comprises more than 300 publications, and he has written, edited or co-edited six books. More important than the quantity of this output is the quality. He has been an important pioneer in the story of glucose-6-phosphate dehydrogenase deficiency and other red blood cell enzyme deficiencies causing hemolytic anemia. He has invented some useful fluorescent screening tests for these enzymopathies and has contributed considerable knowledge about iron metabolism. In 1957 he wrote an article on the clinical evaluation of iron stores that is still widely quoted. He has worked extensively on iron enzymes and was the first to show clinically that females are a mosaic of X chromosomes, some chromosomes being active and some not. His work has also included studies on galactosemia and preservation of red blood cells.

He invented a new type of medical career in which he brings ideas and supervision to his superlative laboratory, supervises the work, puts it together on paper and presents it clearly at meetings. He has avoided being overburdened by clinical practice, formal teaching and administra-

*Ralph O. Wallerstein, MD, Chief of Clinical Hematology Division of the Medical Service, San Francisco General Hospital, Clinical Professor of Medicine and Clinical Pathology and Laboratory Medicine, University of California, San Francisco, and Chairman of the Paul M. Aggeler Memorial Committee.

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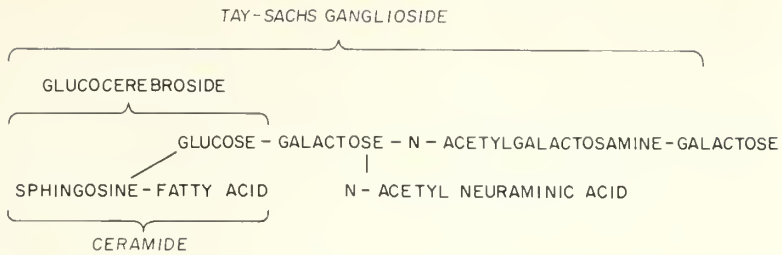

Figure 1.—The structure of a ganglioside. Tay-Sachs ganglioside (G_{M2}) is formed by removal of the terminal sugar. This ganglioside accumulates in patients with Tay-Sachs disease and Sandhoff's disease. If all but one of the sugars are removed, glucocerebroside, the glycolipid of Gaucher's disease, is formed.

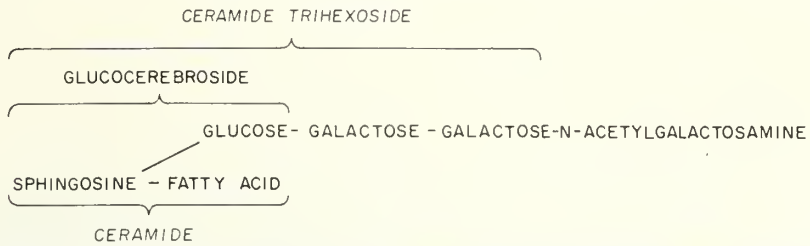

Figure 2.—The structure of a globoside. Removal of all but the first sugar produces glucocerebroside, the glycolipid stored in patients with Gaucher's disease.

ABBREVIATIONS USED IN TEXT

G_{M2} = Tay-Sachs ganglioside
hex = hexosaminidase
CRM = cross-reacting material

tion. Dr. Beutler has recently turned his attention to lipid storage diseases and will address us on recent developments in Tay-Sachs and Gaucher's diseases.

DR. BEUTLER:* I feel very privileged to have been invited to present the Paul Aggeler Memorial Lecture. Paul Aggeler was one of our generation's great hematologists. He was one of those extraordinary persons, encountered only too rarely, whose ability to combine clinical observations and laboratory studies enabled him to advance significantly the frontiers of knowledge. I first met Paul Aggeler in the late 1950's, during my annual January pilgrimage to the clinical meetings in the charming setting provided by Carmel. Paul was always unassuming, friendly and soft spoken, yet his discovery of hemophilia B ranks as one of the milestones in the field of blood coagulation. Because of Paul's devotion to hematology, the privilege of presenting the annual Aggeler lecture has generally been accorded to a hematologist. It is, therefore, with considerable hesitation that I selected the topic for my lecture today. The glycolipid storage diseases are not hematologic disorders in the usual sense of the word. However, because hematology touches so many fields, particularly genetics, the interests of hematologists generally are very broad. I reasoned that Paul would have approved.

I first learned about storage diseases when I entered medical school 30 years ago. Each of these disorders was associated with storage of a chemical substance and with an eponym—the name of the person credited with describing the disease. Remembering which eponym belonged to which chemical was not always easy. Sometimes mnemonic devices were helpful. For example, I knew a young woman whose name rhymed with "Gaucher" and who seemed to have limited intelligence; this served as a reminder to me that Gaucher's disease was the disorder characterized by storage of cerebrosides. The situation is now very different; much has been added to our knowledge of the glycolipid storage diseases. In the past decade and a half there has been a virtual avalanche of progress in the field, and understanding of these disorders is now possible at a molecular level.

All of the glycolipid storage disorders seem to have a similar pathogenesis. The complex glycolipids, gangliosides and globosides (Figures 1 and 2) are constantly turned over by normal cells.

*Ernest Beutler, MD, Chairman, Division of Medicine, and Director, Department of Hematology, City of Hope Medical Center, Duarte, California.

Their catabolism requires that the sugars that comprise their carbohydrate portion be hydrolyzed one at a time, starting at the distal end. Each sugar is removed by an enzyme that is specific both for the sugar and for the type of linkage (α or β) in which it is attached. Deficiency of one of these hydrolytic enzymes results in accumulation of its substrate, the ganglioside or globoside degradation product it was intended to catabolize. I will now discuss the studies carried out in our laboratory concerning the biochemical genetics of two general types of glycolipid storage diseases, Tay-Sachs and Sandhoff's diseases in which Tay-Sachs ganglioside or ganglioside monosialate, 2 (G_{M2}) accumulates, and Gaucher's disease in which glucocerebroside is stored.

Tay-Sachs and Sandhoff's Diseases

Tay-Sachs disease and the clinically and pathologically almost identical Sandhoff's disease are progressive neuromuscular disorders that lead to blindness, severe mental retardation and death within the first few years of life. The glycolipid that is stored in this disorder is a ganglioside, G_{M2} (Figure 1). It is apparent that G_{M2} has not just one terminal sugar but two, N-acetylneuraminic acid and N-acetylgalactosamine. Brady[1] and others attempted to resolve the question of which of the two enzymes involved was defective by synthesizing G_{M2} with labeled N-acetylgalactosamine and with labeled N-acetylneuraminic acid. Initially, it seemed likely that a deficiency of one of the neuraminidases was responsible for the disease, because studies with artificial substrates (simple analogs of the ganglioside such as p-nitrophenyl-N-acetylgalactosamine) had shown that normal N-acetylgalactosaminidase (hexosaminidase [hex]) activity was present in the tissues of children dying with Tay-Sachs disease. However, Robinson and Stirling[2] showed that there were, in fact, two separable forms of hexosaminidase in human tissues, hex A and hex B. When Sandhoff[3] and Okada and O'Brien[4] examined hexosaminidase from children with Tay-Sachs disease for these two specific isoenzymes, striking results were obtained. Children with Tay-Sachs disease had increased activity of hex B, but hex A activity could not be detected. A few non-Jewish children with a particularly severe form of Tay-Sachs disease were found to lack both hex A and hex B; their disease was designated Sandhoff's disease. Recognition that Tay-Sachs disease was due to a deficiency of hex A was a finding of great potential practical importance. Tay-Sachs disease is an autosomal recessive disorder, which has a high frequency among Jews of Eastern European ancestry. Measuring the hex A content of the serum of prospective parents could identify the heterozygous state and thereby make possible detection of couples whose fetuses were at risk of developing this dreadful disorder. Diagnosis by amniocentesis was possible, and selective abortion could be offered to the parents.[5]

Heterozygote detection, however, is not simple when it is necessary to depend solely on the level of activity of an enzyme. Others factors cause considerable variation, and overlap is encountered between the levels in putative normal and putative heterozygous persons. If the cutoff point for the differentiation of heterozygotes from normal persons is too high, many normal women might undergo amniocentesis unnecessarily. If it is too low, some parents who had been reassured by the results of prenatal testing would suffer the agony of having a child with Tay-Sachs disease.

My own interest in the biochemical genetics of Tay-Sachs disease was stimulated by this vexing and potentially important problem. As a hematologist it occurred to me that a similar problem had been encountered in the diagnosis of hemophilia and that the solution might be applicable. Zimmerman, Ratnoff and Littell[6] measured the ratio of Factor VIII procoagulant activity to Factor VIII antigen in the plasma. Because patients with hemophilia usually produce immunologically active but functionally inactive Factor VIII, the plasma of carriers was found to have more immunologic than procoagulant activity. If patients with Tay-Sachs disease synthesized an immunologically detectable and catalytically inactive hex A, the ratio of hex A to hex A antigen would be a much more sensitive way to detect heterozygotes for this disorder. Another reason for undertaking studies of Tay-Sachs disease was a more academic one. How could it be that one autosomal recessive disorder produces a deficiency only of hex A, whereas in other families an autosomal recessive disease produces a deficiency of both hex A and B? There were several theoretic explanations, but which was the right one?

Working with Dr. S. K. Srivastava in our laboratory we first purified hex A and hex B to homogeneity. Human placenta served as suitable starting material, and we were able to immunize rabbits against the homogeneous material. Im-

munoelectrophoresis showed us that little or no cross-reacting material (CRM) was present in the place of hex A in livers of children dying of Tay-Sachs disease[7] (Figure 3). This finding made it appear unlikely that we would be able to apply the strategy used in diagnosing hemophilia carriers to the problem of Tay-Sachs disease. However, our curiosity about the relationship between hex A and hex B had not yet been fulfilled. Study of the antibody against these two enzymes provided us with our first insight into their relationship. Not only were they related genetically, in that a single gene produced deficiency of both enzymes in Sandhoff's disease, but they were also closely related immunologically. The antiserum that we produced against hex A reacted with hex B, and the antiserum that we produced against hex B reacted with hex A.[8] We succeeded in absorbing anti-hex B activity from serum produced against hex A. The absorbed serum was still able to react against hex A (Figure 4). Thus, we concluded that hex A had antigenic determinants that were absent from hex B. On the other hand, we learned that anti-hex A activity could not be removed from antiserum raised against hex B without loss of its capacity to react with hex B as well. These studies led us to suggest that hex A had one subunit, which we designated "α," that was not present in hex B, and that hex A had another subunit, "β," that was represented in hex B. Because the molecular weight of the two enzymes seemed to be identical,[9] the simplest representa-

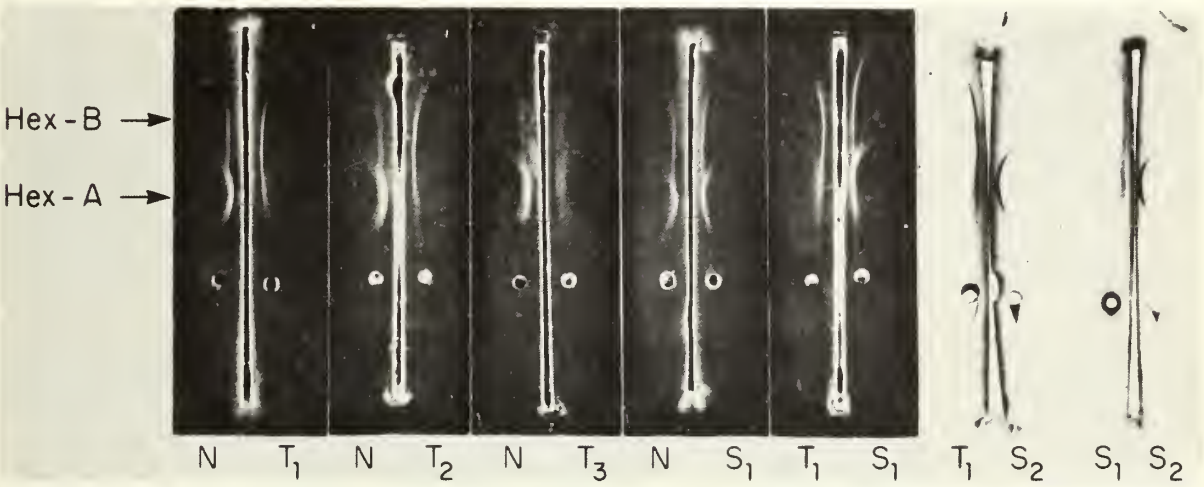

Figure 3.—Immunoelectrophoresis of normal liver extract (N), extract from livers of three unrelated patients with Tay-Sachs disease (T_1, T_2, T_3), and liver extracts from two unrelated patients with Sandhoff's disease (S_1, S_2). (Reproduced by permission from Srivastava and Beutler[7]).

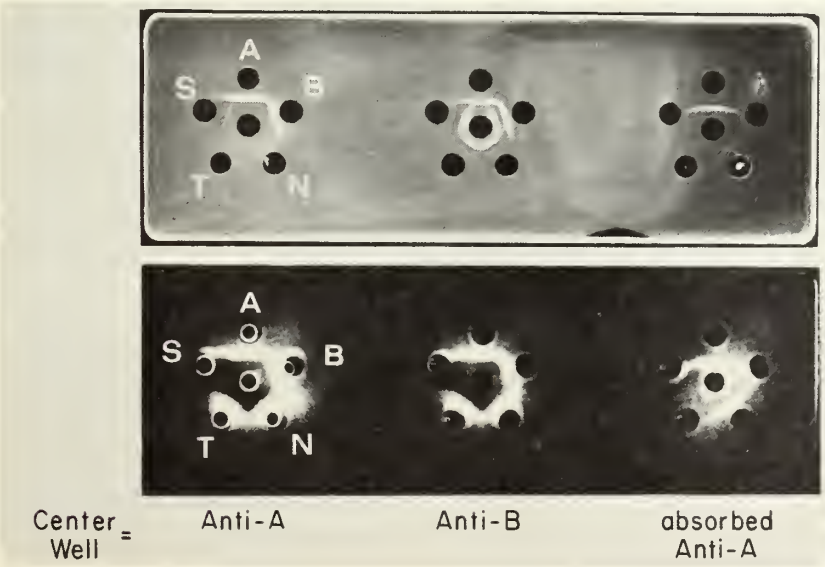

Figure 4.—**Upper,** Immunodiffusion of purified enzyme and liver extracts against antisera (central wells) against hex A, against hex B and against A treated with hex B (absorbed anti-A). **Lower,** same gel stained for hexosaminidase activity.

tion of their structure was that hex A was $\alpha\beta$ and that hex B was $\beta\beta$.

One previously published observation seemed to conflict with this interpretation, however. It had been reported that hex A could be converted to hex B by treatment with neuraminidase.[10,11] Although we were unable to confirm this observation, we did note that as hex A solutions were incubated, traces of hex B appeared to form. The interpretation of these data was clarified when we saw a report that indicated that even heat-inactivated neuraminidase preparations had the capacity to convert hex A into hex B.[12] Apparently, something else in neuraminidase produced the conversion, and we quickly established that it was the Merthiolate® that had been added as a preservative.[13] p-Hydroxymercuribenzoate has long been used to dissociate hemoglobin chains, and it seemed reasonable that similar chain dissociation might be accomplished with other mercurial compounds such as Merthiolate. We proposed[14] the following schema to account for the effect of Merthiolate in producing hex B from hex A:

$$\underset{\text{Inactive}}{\alpha \text{ or alkylated } \alpha} \leftarrow \underset{\text{hex A}}{(\alpha\beta)_n} \rightarrow \underset{\text{hex B}}{(\beta\beta)_n}$$

If Merthiolate produces the conversion by dissociating the α and β subunits of hex A, with subsequent reassociation of β subunits to form hex B, we should be able the find the α subunit. Indeed, we were able to separate an alkylated dimeric α subunit from pure hex A preparations that had been treated with Merthiolate or p-hydroxymercuribenzoic acid.[15] Recently, an anti-α chain serum has been produced by immunizing rabbits with such α-chains after their treatment with glutaraldehyde.[16]

Definitive proof of the subunit structure of hex A and hex B was achieved through study of the tissues of a patient with Sandhoff's disease. As had previously been noted by others, a small amount of residual hexosaminidase activity could be identified in such persons and was designated hex S[17,18] (Figure 5). According to our subunit model, patients with Sandhoff's disease are unable to form functionally adequate β-chains, and thus the residual enzyme activity in Sandhoff's disease might be attributed to polymerized α-chains. The observation that hex S was made up of α-chains was verified immunologically; it reacted with anti-A but not with anti-hex B serum.[18] Because hex S was a homopolymer of α-chains and hex B a homopolymer of β-chains, it should be possible

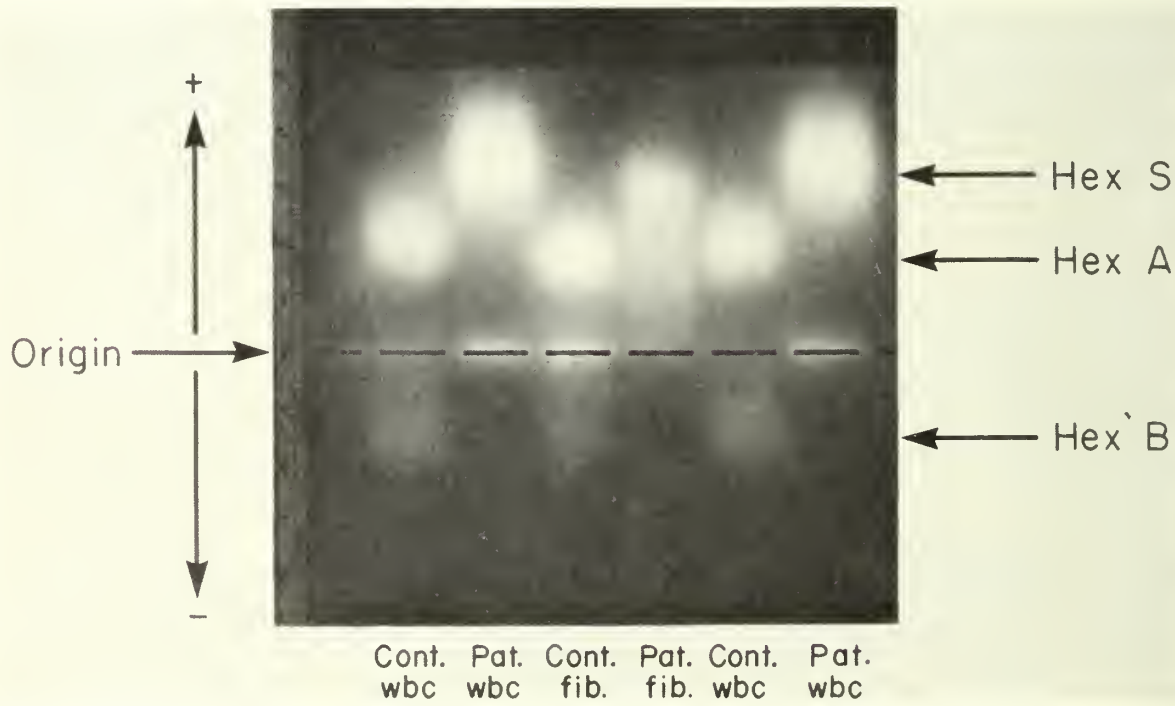

Figure 5.—Starch gel electrophoresis at pH 6.0 of fibroblasts (fib.) and leukocytes (wbc) from normal subjects (Cont.) and a patient (Pat.) with Sandhoff's disease.[18] Extracts containing approximately equal amounts of hexosaminidase were placed in the slots, and the gels were stained for hexosaminidase activity. Hex A and hex B are missing from the cells obtained from a patient with Sandhoff's disease. Instead, a rapidly moving band, designated as hex S, was present. This band represents α-chain polymers.

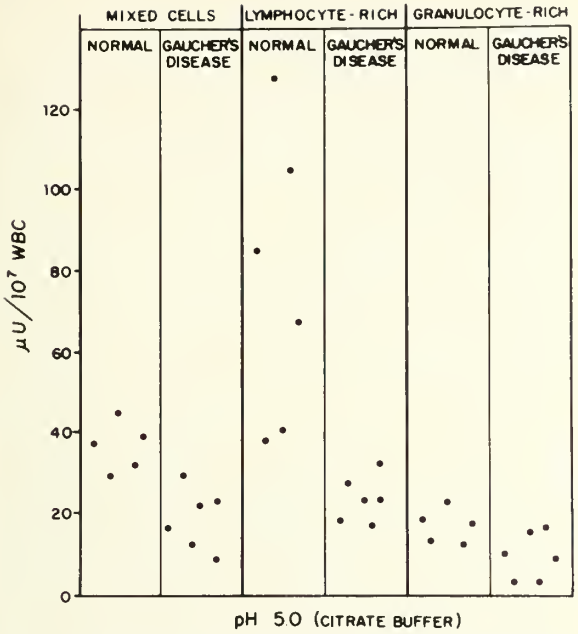

Figure 6.—β-Glucosidase activity of leukocytes from normal subjects and patients with Gaucher's disease. The assays were carried out at pH 5 with 4-methylumbelliferyl-β-D-glucopyranoside as substrate. At this pH, poor discrimination between normal and Gaucher's disease subjects was achieved.

to produce hex B and hex S from hex A, and to produce hex A from hex B plus hex S. This, too, was accomplished.[19]

A striking similarity is apparent between the hexosaminidase system and the thalassemias. In both α-thalassemia and Tay-Sachs disease, a deficiency in α-subunits results in polymerization of β-subunits. In α-thalassemia, hemoglobin β chains form hemoglobin H; in Tay-Sachs disease, hexosaminidase β chains polymerize to form increased amounts of hex B. In both α-thalassemia and Sandhoff's disease, an excess of α-chains is found. The α-hemoglobin chains in β-thalassemia apparently damage the cell membrane. The α-hexosaminidase chains aggregate in Sandhoff's disease to form hex S.

Gaucher's Disease

Gaucher's disease is a particularly prevalent glycolipid storage disease, occurring at a frequency of 1:5,000 to 1:10,000 Jewish births. In the most common adult variety of Gaucher's disease, gradual progressive storage of glucocerebroside in liver, spleen and bone marrow results in pancytopenia, hepatic failure and pathologic fractures. The enzymatic defect in Gaucher's dis-

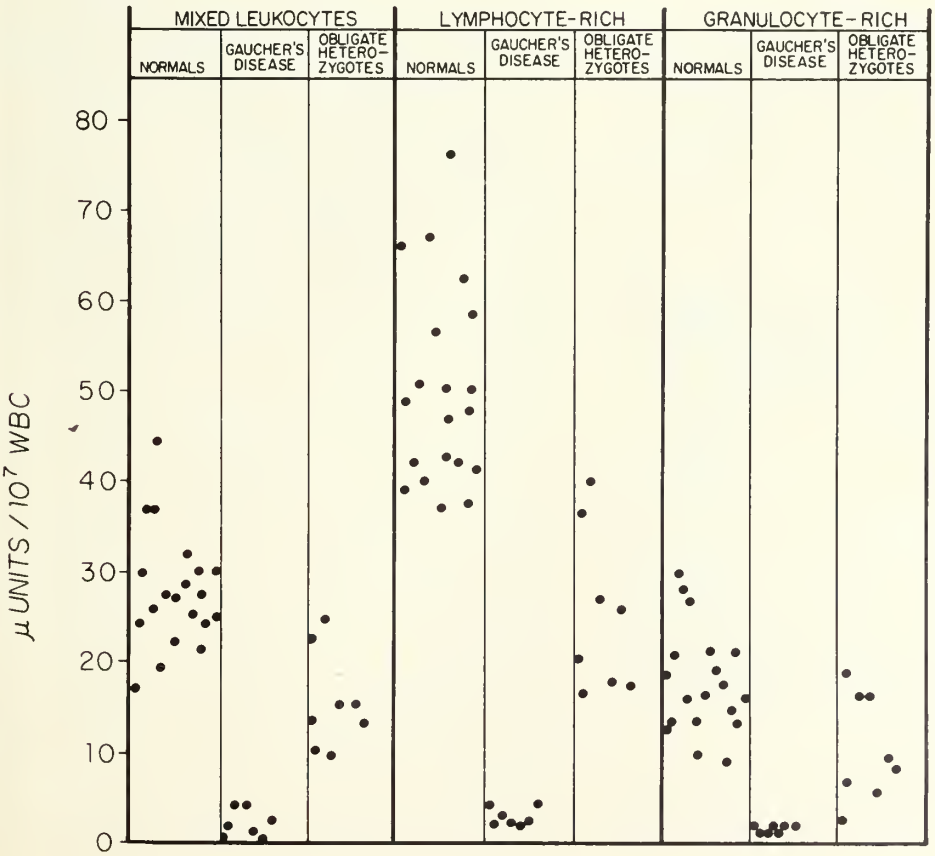

Figure 7.—β-Glucosidase of leukocytes of normal subjects, patients with Gaucher's disease, and obligate heterozygotes. The assays were carried out at a pH of 4 with 4-methylumbelliferyl-β-D-glucopyranoside as substrate. Excellent discrimination between the different genotypes was achieved at this pH. (Reproduced by permission from Beutler E and Kuhl W: J Lab Clin Med 76: 747-755, 1970.)

ease has been identified as a deficiency in glucocerebrosidase.[20] Localization of the glycolipid in the reticuloendothelial system makes Gaucher's disease a particularly attractive target for replacement therapy.

The first problem that we faced in 1969 as we began to study the biochemical genetics of Gaucher's disease was that the radioactively labeled glucocerebroside used to show enzyme deficiency existed in only one laboratory and was not available to us. Its synthesis was complex and it was by no means certain that it could be carried out successfully again. However, the use of an artificial analog of glucocerebroside, 4-methylumbelliferyl-β-glucopyranoside for study of this disorder had recently been described,[21] and this material was commercially available. Because it seemed possible that the artificial substrate measured enzymes other than glucocerebrosidase, W. Kuhl attempted to determine whether or not patients with Gaucher's disease lack this activity. Because leukocytes were the most readily available cells and because examination of these cells might also lead to detection of the heterozygous state, they were chosen for study. Our initial results were disappointing (Figure 6). Assaying β-glucosidase at pH 5, the pH generally chosen for the assay of acid hydrolases, we found little differences in the β-glucosidase activity of normal leukocytes and those from Gaucher's patients.

To determine whether or not a major qualitative difference existed between the β-glucosidase of Gaucher's cells and normal cells, we investigated some of the properties of leukocyte β-glucosidase using an approach similar to that employed in investigating a glucose-6-phosphate dehydrogenase mutant. The pH-activity curves of β-glucosidase from normal subjects showed a pH optimum of approximately 5, which was identical to that of patients with Gaucher's disease. We discovered, however, that a second and lower pH optimum was present in normal leukocytes and that the enzyme activity at this latter pH of 4.0 was missing from the leukocytes of patients with Gaucher's disease. If we assayed the enzyme at pH 4,[22] clear distinction between the leukocytes from patients with Gaucher's disease and normal persons was possible (Figure 7). It was also possible to identify heterozygotes for Gaucher's disease with reasonable confidence by using a lymphocyte-rich preparation of leukocytes. Some overlap was present, due in large part to the higher enzyme activity in monocytes than in lymphocytes. The lymphocyte preparation also contained monocytes, and its activity was therefore influenced to a pronounced degree by the extent of contamination with these cells. Layering suspensions of the lymphocyte-rich fractions on plastic Petri dishes allowed us to separate lymphocytes from monocytes; the latter attach to the plastic surface. Now it was possible to better differentiate normal from heterozygous subjects.[23]

Similar results were obtained in a study of cultured fibroblasts. Here, too, use of the artificial substrate, 4-methylumbelliferyl-β-glucopyranoside permitted differentiation of Gaucher's disease from normal and from heterozygous subjects. Amniotic cells also contain β-glucosidase activity, and the identification of fetuses with Gaucher's disease is now possible.

The ultimate aim of our study, however, has been the development of improved methods for the treatment of patients with Gaucher's disease. No specific therapy is available and management of patients with this disorder is currently a frustrating experience. One of the most frequently encountered complications of Gaucher's disease is thrombocytopenia. Splenectomy invariably produces normalization of the platelet count but does not reduce the amount of globoside that the body must metabolize each year. Instead of being sequestered relatively harmlessly in a gradually enlarging spleen, the glycolipid now accumulates in liver and bone.

Dr. Robert Yonemoto, of the Department of

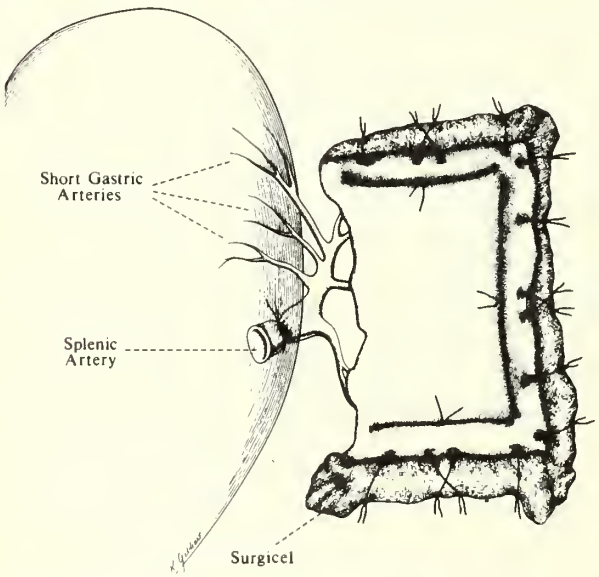

Figure 8.—Partial splenectomy according to the procedure used by Dr. Robert Yonemoto, City of Hope Medical Center.

Surgery at the City of Hope, has successfully carried out a partial splenectomy in a patient with Gaucher's disease. The portion of the upper pole of the spleen supplied by the short gastric vessels was preserved, and bleeding from the cut edges was controlled with fibrin foam and mattress sutures (Figure 8). Complete remission of the patient's thrombocytopenia was achieved. We hope that the small piece of spleen left behind will prosper and enlarge, continuing to accumulate glycolipid and thereby protecting the patient's liver and bones from damage. However, partial splenectomy may, at best, provide only a limited solution to some of the problems associated with Gaucher's disease.

More promise lies in replacement of the missing enzyme. Unfortunately, glucocerebrosidase has proved to be extraordinarily difficult to purify, largely due to its firm attachment to the lysosomal membrane and our consequent inability to solubilize it. Pentchev and co-workers[24] succeeded in carrying out partial purification of glucocerebrosidase in a detergent-soluble form. The enzyme was precipitated on serum albumin and administered to several patients.[25] The yield was extremely low, limiting the amount that could be administered. Although transient decreases of glucocerebroside levels in red blood cells were observed, no clinical improvement was recorded.

Dr. George Dale in our laboratory recently succeeded in developing a high-yield, relatively rapid method of purifying soluble β-glucosidase from human placenta.[26] Earlier attempts to solubilize the enzyme by preparing acetone powders from placenta had resulted in loss of all enzyme activity. Dr. Dale's discovery that β-glucosidase has an absolute requirement for acidic phospholipid[27] immediately explained our earlier failure. We found that treating placental extract with organic solvents such as acetone or ethanol does release the β-glucosidase in soluble form, but that activity can only be measured in the presence of added phospholipid. With the solubilization of β-glucosidase, further purification by conventional and affinity techniques became possible.[28]

A delivery system is needed to bring the enzyme to the stored glycolipid. Several methods have been proposed, but one of the simplest appears to be enclosure of the enzyme in the patient's own red blood cells.[29] When erythrocytes are lysed in hypotonic solution, resealing can be effected by incubation in isotonic saline. Such lysis and resealing is most easily carried out in dilute suspensions of erythrocytes, but this would be much too wasteful of the precious enzyme purified from many kilograms of placenta. We therefore added the purified enzyme to packed erythrocytes in a cell dialysis bag, dialyzing first against a 5 mM potassium phosphate buffer, pH 7.4. The dialysis bath was then replaced with a phosphate buffer containing 0.9 percent sodium chloride, and the mixture was warmed to 25°C. After two hours, the resealed erythrocytes were washed. Usually 15 to 30 percent of the enzyme was entrapped within erythrocytes.

We have undertaken experimental enzyme replacement therapy in one patient with far-advanced Gaucher's disease. The first course of treatment, three injections of resealed cells containing a total of 560 mUnits of enzyme, was carried out in April 1976. In July 3,700 mUnits of enzyme were directly administered intravenously as two injections. Finally, in September another 2,200 mUnits of enzyme were administered, again in erythrocytes—but those which were coated with anti-Rh antibody to facilitate their clearance from the circulation.

In the complex setting of far-advanced Gaucher's disease, the results of therapy are not easy to evaluate. Intercurrent infections and other complications tend to obfuscate the results. However, it was clear that enzyme therapy was well tolerated; no untoward reactions were experienced by the patient during any of the courses of treatment. At the onset of therapy, the patient's liver was the same size as had been recorded eight years previously. During the six months of enzyme therapy, some decrease in the size of the liver appeared to occur; the hepatic margin, identified by palpation, regressed 3 to 6 cm. Visualization of the liver with sulfur-technetium colloid in 1968 showed there to be major areas in which the radionuclide was not taken up. These areas had enlarged somewhat before enzyme replacement therapy was started. At the end of six months of treatment, hepatic uptake of colloid had greatly improved, so that the liver scan had a much more normal homogeneous appearance. Each course of enzyme therapy was associated with a rapid increase in the platelet count which lasted for several weeks. There seemed to be some increase in the overall sense of well-being. Further observation of this patient and other patients whom we plan to treat will be required to delineate the possible role of enzyme replacement in the management of patients with Gaucher's disease.

The treatment of glycolipid storage diseases by the administration of exogenous enzyme represents the type of interaction between basic science and clinical medicine that was one of the outstanding features of Paul Aggeler's professional career. It is for this reason that I considered these studies to be an appropriate theme for this year's Paul Aggeler Memorial Lecture.

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Important Advances in Clinical Medicine

Epitomes of Progress—Urology

The Scientific Board of the California Medical Association presents the following inventory of items of progress in urology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in urology which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Urology of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, California Medical Association, 731 Market St., San Francisco, CA 94103

Transpubic Urethroplasty for Membranous Urethral Strictures

REPAIR OF traumatic stricture of the membranous urethra is a significant surgical challenge because of the relatively inaccessible location of this portion of the urethra behind the symphysis pubis. Transpubic surgical operation was first applied to posterior urethral strictures in 1962, when Pierce used total pubectomy, but this approach has more recently been popularized by Waterhouse. The proposed advantages of this approach are its superior exposure and its applicability to strictures more than 1 cm in length.

The surgical objective is to bypass the stricture anteriorly. After removal of a trapezoidal piece of pubic bone, the distal urethra is mobilized, spatulated and anastomosed to the anterior prostatic urethra at its apex. The prostate is not mobilized and the stricture is not excised.

Transpubic urethroplasty has been successfully carried out in patients with membranous urethral strictures secondary to pelvic fractures with disruption of the prostatic-membranous urethra, strictures following transurethral external sphincterotomy and stricture due to a compromise of the membranous urethra during radical retropubic prostatectomy.

The transpubic approach to membranous urethral strictures affords superior exposure and allows a direct, undervision and tension-free anastomosis. Wedge resection of the pubis is recommended over symphysiotomy and separation of pelvic bones, which may cause pelvic pain and instability. Operative blood loss can be significant and bleeding is difficult to control until the wedge of pubis is removed. The level of urinary control may be lost if prostatectomy has been carried out in a patient or subsequently is required, unless the bladder neck remains intact. The use of a pedicle graft of omentum, placed over the anastomosis, may improve the success

rate of this approach. Transpubic surgical operation provides excellent exposure with minimal morbidity and offers a direct approach to membranous urethral strictures.

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Morales P, Littmann R, Golimbu M: Transpubic surgery—A new approach to difficult pelvic operations. J Urol 110:564-570, Nov 1973

Urinary Lysosomal Enzymes for Early Detection of Renal Allograft Rejection

THE RELEASE of lysosomal enzymes into the urine, the result of cellular damage caused by rejection of a renal allograft is a valuable sign of early rejection.

Patients who received renal allotransplants have been monitored to compare the sensitivity of urine levels of β-galactosidase and N-acetyl-β-glucosaminidase. Using conventional clinical and laboratory measurements to detect impending rejection, a rapid (60 minute), simple, accurate, fluorometric assay was used to measure activity of both enzymes. Eighty percent of 32 rejection episodes were accompanied by a two-to-six-fold increase in enzyme release. Increases in serum creatinine and decreasing urine volumes occurred in 26 rejection episodes. In 12 episodes, elevated urinary enzyme levels were observed as early as four days before clinical evidence of rejection.

Rejection episodes, modified by high-dose administration of corticosteroids, were mirrored by a corresponding decrease in enzymatic activity.

It is postulated that urinary lysosomal enzyme measurements by fluorometric assays are valuable indicators of acute renal rejection, particularly when the diagnosis is not clearly established by conventional criteria. The accuracy of this rapid test makes it particularly appealing in the evaluation of renal allotransplantation rejection episodes.

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Complications of Urinary Undiversion

COMPLICATIONS of urinary undiversion may be divided between those related to patient selection and those pertaining to the operation. A detailed understanding of the anatomic and physiologic alterations in the dynamics of urine transport is an essential prerequisite for the selection of suitable candidates. The diverted urinary system, which is intended primarily for conduit function, is substantially changed to include reservoir function and must, therefore, be amended to provide efficient urine transport, an antireflux mechanism, adequate capacity, continence and complete emptying. In addition, the reconstructed system must be able to handle the mucus generated by the interposition of an intestinal segment. The implications of these hydrodynamic alterations, particularly in a patient with compromised renal function, may be profound.

The potential life-threatening hazards of urinary reconstruction demand rigid assessment of potential candidates and satisfactory demonstration of functional ability and stability of renal function by the singular measures of excretory urography and serum creatinine studies. The lower tract must be carefully evaluated and those factors that originally necessitated supravesical diversion must be recalled and carefully reassessed. Contraindications to undiversion include patients with continued renal deterioration or with creatinine clearance less than 40 ml per minute. Neurogenic bladder represents a relative contraindication.

When the proper operation is done correctly in a carefully chosen patient, the end result can be encouraging. Because of the precarious and delicate renal and metabolic balance involved, both the patient and the surgeon must recognize that the operation may either succeed brilliantly or fail dismally. The application of strict guidelines for patient selection and meticulous attention to intraoperative detail should help to tip the balance toward success.

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The Use of Aldomet® (alpha methyl dopa) In the Treatment of Neurogenic Bladder

PATIENTS SUFFERING from neurogenic bladder dysfunction (upper neuron and lower neuron lesion) have been treated with Aldomet® (alpha methyl dopa) to cause relaxation of the pelvic floor. Patients most suitable for this therapy are those with good bladder capacity and high residual urine. Aldomet's mechanism of action is probably central (acting through the main metabolite alpha-methylnorepinephrine). This substance stimulates alpha-inhibitory receptors in the supraspinal centers, blocking the sympathetic activity. This effect will facilitate bladder contraction and reduce urethral resistance.

The minimal side effects, the familiarity of the medical community with the use of this drug and its effectiveness in upper neuron lesion patients make Aldomet another drug useful in the urological armamentarium.

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Raz, S, Cain M: Adrenergic receptors in the female canine urethra. Invest Urol 9:319-323, Jan 1972

Value of Saralasin Test in Detection of Human Renovascular Hypertension*

PATIENTS WITH renovascular hypertension can be distinguished from most patients with essential hypertension by the use of a new drug, saralasin (1-sar-8-alatangiotensin II) (Eaton Laboratories, Norwich, New York). Saralasin acts by specific competitive inhibition of angiotensin II at receptor sites. In this study it was administered intravenously before and after furosemide-induced salt depletion.

In patients with subsequently confirmed renovascular hypertension, blood pressure decreased toward normal after saralasin administration. The depressor effect could be discerned readily with standard monitoring equipment ten minutes after a large bolus injection of the drug; or the effect could be sustained for longer periods by continuous infusion of the drug. In some patients with renovascular hypertension there were elevated peripheral renin levels or lateralizing renal vein renin ratios, or both; however, in several others these were not present. Yet all of the patients responded to saralasin administration. Thus the basic pathophysiology of renovascular hypertension was correctly identified by saralasin responsiveness, but not always by the renin determinations.

In patients with essential hypertension or incidental stenoses, usually no lowering of blood pressure occurred after saralasin administration. However, in the occasional patient with high-renin essential hypertension, the response to saralasin was similar to that seen in patients with renovascular hypertension. Thus the saralasin test is specific not for renovascular hypertension per se, but for renin-mediated hypertension.

The saralasin test appears to be of greatest value as a rapid screening procedure to help determine in which hypertensive patients further search for a renovascular cause should be carried out. The saralasin test may also be used to justify operation in patients in whom hypertension, severe renal artery stenoses and equivocal renin data are noted. The test appears to be completely valid and safe provided (1) administration of other antihypertensive medication is discontinued beforehand, (2) the patient is mildly salt-depleted and (3) genuine hypertension is present at the time of the test.

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*From a study published in full in the October 1976 issue of the *Journal of Urology*.

Experience with the Transverse Colon Conduit for Supravesical Urinary Tract Diversion

TRANSVERSE COLON conduit urinary diversion has been used in patients in whom extensive prior pelvic irradiation therapy has been done. Carcinoma of the urinary bladder and uterine cervix were the most common primary diseases for which irradiation therapy was administered. Indications for urinary diversion included severe

radiation cystitis, vesicovaginal fistula with or without residual malignancy, and ureteral obstruction.

This type of diversion affords the use of non-irradiated bowel as well as the ureter above the field of irradiation. Single layer end-to-side ureterocolic anastomoses were constructed without the use of antireflux techniques or ureteral stents. Complications were related to the patients' general condition and prior irradiation as well as to specific technical problems. Complications requiring additional surgical procedures included ureterocolic extravasation and obstruction, abdominal wound dehiscence, stomal prolapse and peristomal hernia.

Patients with preoperatively normal upper urinary tracts remained normal following diversion. Patients with unilateral or bilateral ureteral obstruction preoperatively tended to improve. The transverse colon conduit has been free of stomal stenosis, renal function changes or high residual urine volumes and should be considered the preferred intestinal segment for use in patients with extensive pelvic irradiation therapy.

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Avascular Renal Adenocarcinoma: Variations and Characteristics

THE CHARACTERISTIC NEOVASCULARITY seen in patients with renal carcinoma is absent in 10 percent of patients with this neoplasm. These tumors frequently simulate benign lesions and have varied diagnostic characteristics. All modalities including intravenous pyelography, nephrotomography, ultrasonography, cyst puncture with cystic fluid assessment, angiography and operation with tissue specimens submitted for pathologic examination may be required before diagnosis is established. An orderly approach to the evaluation of lesions will allow accurate diagnosis approaching 100 percent with minimum morbidity. Attention to the finer details of vascular patterns on angiography has proved to be a very helpful diagnostic aid. Suspicion of carcinoma increases if, on a selective angiogram, there is (1) thickening of the "cyst" wall, (2) a rim vessel following the circumference of the lesion, (3) pericystic or capsular vessels entering an otherwise avascular mass, (4) increased vascularity of the parenchymal border and (5) contrast pooling, even to a minor degree, in a lesion on a delayed nephrogram. If aspiration of the tumor is done, histochemical, cytologic and radiographic examinations are necessary to diagnose these elusive lesions.

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Very Selective Renal Vein Renin Determination in the Diagnosis of Segmental Renal Hypertension

CATHETERIZATION of the main renal vein for renin assay is valuable in determining the clinical significance of a renal abnormality in a hypertensive patient. However, findings from main renal vein catheterization can be misleading in the presence of renin producing lesions that do not affect the whole kidney. Dilution of renin-rich segmental blood in the main renal vein, incomplete mixing or "streaming," and the presence of an accessory renal vein are reasons that a significant ratio is not found.

Catheterization of segmental renal veins should improve the accurate detection of renin mediated hypertension. We use bilateral, small diameter catheters, preshaped for upper and lower pole segmental vein placement, and have consistently obtained blood from any area of interest within a kidney. Simultaneous samples are obtained from both the normal and the abnormal portion of the kidney. Sampling error is reduced since the catheter tip is not easily dislodged from a small vein when the kidney moves with respiration or by change of position of the patient. The failure to catheterize a portion of a kidney alerts the angi-

ographer to search carefully for an accessory vein that drains directly into the inferior vena cava. There have been no complications noted with this technique.

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Korobkin M, Glickman MG, Schambelan M: Segmental renal vein sampling for renin. Radiol 118:307-313, Feb 1976

Clinicopathologic Features of Unsuspected Lymph Node Metastases in Prostatic Carcinoma

PELVIC LYMPHADENECTOMY is an important diagnostic tool in the accurate staging of patients with prostate cancer. In one study of 62 patients with clinical stage B_1, B_2 or C prostatic cancer, the cellular differentiation of the primary tumor and the extent of involvement of the prostate by the carcinoma correlated significantly with the incidence of unsuspected pelvic lymph node metastases. Using Mostofi's AFIP [Armed Forces Institute of Pathology] fascicle histologic classification system, 39 of the 62 patients had differentiated tumors and 23 had undifferentiated tumors. Eighteen tumors were Grade I, 39 were Grade II and 5 were Grade III. While in only 20 percent of patients with differentiated tumors were nodal metastases present, 56 percent of those with undifferentiated tumors had metastases. Similarly, while an average of only 46 percent of the sections of prostate contained tumor in the patients without metastases, an average of 65 percent of the sections were involved by carcinoma in those patients who did have nodal metastases. All patients in whom less than 35 percent of the prostate sections were involved by tumor were free of metastases.

Although not statistically substantiated, there is a correlation between anaplasia and incidence of metastases. Metastases occurred in 22 percent of patients with Grade I, 34 percent with Grade II and 60 percent with Grade III tumors in this series.

No significant effect could be shown in the incidence of unsuspected pelvic nodal metastases for perineural invasion, vascular invasion, capsular invasion, extracapsular involvement or tumor at excisional margins. However, no patient had metastases unless a tumor had extended at least halfway through the capsule. Combining two histologic features resulted in correlations with incidence of nodal metastases less significant than using one of the variables singly.

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EDITORIALS

WJM Welcomes Nevada

WITH this issue THE WESTERN JOURNAL OF MEDICINE becomes the official journal of the Nevada State Medical Association and its members join the membership of the California and Idaho Medical Associations in receiving this journal as a benefit of membership in these associations. The Nevada and Idaho editions of WJM may from time to time contain additional material of particular interest to the members of those state associations but which may be of less interest to members in another state. Contributions from all three states are welcome and are given equal consideration by the Editorial Board—which is broadly representative of all the western states.

It is just three years since *California Medicine* entered its chrysalis and emerged as THE WESTERN JOURNAL OF MEDICINE. Long (since 1902) the voice of medicine in California, it aspired to reflect the vitality and achievements in science, education and practice which are the marks of medicine in the western United States; in a stronger presence in the medical literature which records and shares advances and progress with the medical community in the nation and indeed the world.

The WESTERN JOURNAL seeks to offer a variety of fare for its readers and to be truly a useful journal. Besides material useful to practitioners, it seeks also to have something of interest for students, academicians, researchers and even for the political leaders of our profession. The circulation is growing, with subscribers in every state of the Union and not a few from abroad. The editors, the Editorial Board and many others are dedicated to making this journal a regional instrument of physician education and continuing education in the West, and also to make it an increasingly distinguished journal on the national scene.

We welcome the Nevada State Medical Association to the WJM family of associations and its members to our readership. We look forward to a long and productive association which should be of great benefit to all concerned.

—MSMW

Aminoglycoside Nephrotoxicity

CONFIRMATION IN MAN of findings in animal models relevant to human disease or therapy is exemplified in the case report in this issue by Bennett and co-workers. They are almost the first to show the proximal renal tubular abnormalities due to aminoglycosides previously shown in rats and are the first to document the persistence of these changes as long as six weeks after stopping aminoglycoside therapy. These agents, notably gentamicin, are the most widely used antibiotics in hospitals except for the penicillins and cephalosporins and contribute very materially to the management of Gram-negative bacterial sepsis. All of them (streptomycin, kanamycin, gentamicin, tobramycin, amikacin, neomycin) have two major drawbacks—the development of high level bacterial resistance and a margin between safety and toxicity far less salubrious than in the case of the penicillins and cephalosporins. Fortunately, early gloomy predictions for a high prevalence of bacterial resistance have been confined largely to small population groups (such as burn units, newborn nurseries and urology wards) and early concern for toxicity has been modified as methods have been appreciated for calculating dosage, monitoring blood levels and detecting early evidence of impaired renal function.

As soon as the first two aminoglycosides, neomycin and streptomycin, were introduced to clinical usage in the mid-1940's, nephrotoxicity was evident—serious and frequent with neomycin, rare and almost confined to patients with preexisting renal impairment with streptomycin. Early pharmacologic studies established the linear relationship between creatinine or inulin clearance and aminoglycoside excretion and most physicians probably regard their elimination as a simple filtration process without participation of the renal tubule. Insufficient attention may have been paid to the pathology of aminoglycoside toxicity in animals which identified the proximal renal tubular cells as a primary target, and the ability of diuretic agents which act primarily on tubular cell function such as furosemide and ethacrynic acid to enhance aminoglycoside nephro-

toxicity (as well as ototoxicity). The nephrotoxicity from gentamicin which was encountered by Jao and Jackson[1] during the treatment of their first few patients seriously retarded the clinical investigation of this antibiotic. It provided, however, the stimulus for the first intensive study of a nephrotoxic agent, at least among the antimicrobials, not because gentamicin was more nephrotoxic than other drugs but because it had the potential for such extensive usefulness and because it came on the scene at a time when the orientation for such study was ready. In general, two clinical types of nephrotoxicity, probably related pathophysiologically, have been associated with the use of gentamicin in man. The first is manifested by a gradual rise in serum creatinine levels, usually promptly reversible on discontinuation of the drug. This occurs in approximately 5 percent of patients receiving gentamicin and is probably related to daily dosage among other factors. The second type is acute renal failure associated with a sudden drastic decrease in renal function, usually oliguria and, finally, a diuretic phase with recovery of renal function (usually less than before the oliguric episode). This type usually occurs in patients with sepsis who may be hypotensive and often are receiving multiple drugs so that the causation of the renal failure appears to be multifactorial. Neither type of nephrotoxicity has been directly related to serum gentamicin concentrations, which is not to say that some sort of relationship does not exist.[2]

Residues of aminoglycosides in tissues, especially the kidney, for several weeks after treatment of animals used for food by man have been recognized for many years and have been the basis for establishing drug withdrawal times before animal slaughter.[3] After administration of the usual therapeutic doses of dihydrostreptomycin to sheep or cattle for only four days, residues of 1 to 1.5 μg per gram of kidney can be demonstrated 45 to 60 days after the last injection. Treatment of poultry for only two days may result in a renal residue of 1 to 2 μg per gram of kidney 10 to 20 days later. It is, therefore, not surprising that Bennett and co-workers should report for the first time important confirmation of these findings in man with 30 μg of gentamicin per gram of kidney removed by open biopsy six weeks after the last injection of the antibiotic. Ezer and associates[4] have shown that various organs, including muscle, bind aminoglycosides although the concentration is higher in the renal cortex than elsewhere. Whether this is due to a special affinity of the renal cortical tissues for the drug or merely that this tissue is exposed to the unusually high concentration which appears in the renal tubular urine may be in some question since the tissue binding is concentration dependent. Along this line, Berendt and Walker[5] showed that administration of kanamycin by aerosol to rats resulted in extremely high concentrations in lung tissue with levels over 6 μg per gram of lung persisting for at least 96 hours after the last exposure. The degree of renal cortical binding varies with different aminoglycosides and the question has been raised whether this might have a relationship to nephrotoxicity. The correlation does not appear to be perfect but the need for a less cumbersome method than whole animal pharmacology to determine relative toxicity has never been greater because new aminoglycosides are being created by molecular manipulation similar to the productive results with the penicillins and cephalosporins.

Bennett and co-workers have also confirmed in man the ultrastructural changes first shown by Kosek and co-workers, mainly in the proximal renal tubular cells of Fisher 344 rats, a strain that appears considerably more susceptible to these manifestations of cellular injury than Sprague-Dawley rats—a fact, in itself, of some interest since it suggests individual differences in susceptibility to drug toxicity. These anatomical abnormalities are not specific for dysfunction in renal tubular cells nor for aminoglycosides nor even for nephrotoxic antibiotics generally since they are different from the ultrastructural changes produced by cephaloridine. However, finding that they occur at all after a dose in rats as low as 1 mg per kg of body weight per day and that they persisted in the patient now reported six weeks after the last dose of gentamicin suggest that covert injury or dysfunction may be more common than suspected. The exposure of the renal tubular cells to much higher concentrations of aminoglycosides and persistence of bound drug for a longer time than elsewhere may play some role in these findings. The choice of the word "handling" by Bennett and his associates in stating that their findings "appear incompatible with renal gentamicin handling by glomerular filtration alone" seems particularly appropriate since evidence is not at hand to determine whether active transport or simple diffusion and nonspecific binding is involved. The fact remains that aminogly-

cosides given in the usual nonnephrotoxic doses are not simply filtered by the glomerulus to pass unobstrusively down the collecting system. They accumulate and persist in renal cortical cells. How this process may be related to nephrotoxicity, how the quantitative aspects of the phenomenon may reflect relative nephrotoxicity, what effect aminoglycosides have on the metabolic machinery of the cell and how this might contribute to drug interactions harmful to renal function remain to be determined.

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Medicine and the Certainty of Change in the Coming Century

As we close the bicentennial year and embark upon the third century in the history of America as a nation, there are many uncertainties. In fact about the only thing that is certain is that there will be change. The President-elect has promised change and seems likely to do his best to bring it about. But beyond this it is evident enough that we are entering an era of change which is probably without precedent in history. And also without precedent, medicine finds itself at the focus of much of it.

The forces for change are awesome. Much, perhaps all of these, stem from scientific and technologic progress, which itself is always changing and thus spawning other changes—often most unpredictable ones. Profound societal changes are among these effects. Not only science and technology, but personal and public attitudes are changing, and the traditional social, economic and political systems of our society simply do not seem to be working as well as they did, or could or should. The core problem of our institutional systems seems to be an inability to adapt and adjust rapidly enough to the forces of change and their effects. The problem is inherent in the institutions of both the public and private sectors.

But the forces of change are not likely to slacken. Rather they will increase in both pace and extent. The reality of the closed biosphere is only just beginning to penetrate the national consciousness, and as this occurs during the coming century, there will be a recognition of a new kind of biological interdependence as prerequisite for health, well-being and quality of life for any, or for all. The idea that all life, whether physiological, social, economic or political, goes on within a biological framework, subject to biological law, will follow. And biological law says that every person is different, and that personal maturation and fulfillment are individual matters. It also says that health, well-being, fulfillment and quality of life for any person depends upon a healthy interaction with a physical and social environment which must also be healthy. Consequently, the person and the environment may be expected to assume greater importance in the years ahead, and this is a quantitative if not a qualitative change from what has been the case. It would seem certain therefore that the foreseeable future will bring not only scientific and technological, but social, economic and political change as well.

If substantial and increasingly rapid change is a certainty, then medicine should prepare not only to live with it, but where possible to guide it. Medicine has been a technological success and is now being almost swamped by the problems brought on by attempts to achieve a fair and even distribution of this success to the public. Doctors are still very high in the public esteem. The other great professions suffer by comparison; they are generally held in less esteem by the public.

But all is not well with medicine. It too is showing signs of failure to cope, of confusion and disarray, particularly in social, economic and political matters. It shares this weakness with much if not all of the whole health enterprise. It too lacks effective mechanisms of adapting quickly enough to change whether on the local, state or national level. It has failed to coordinate the technologic, social, economic and political strengths of the health enterprise and to bring

these to bear to identify and define the problems of health care delivery, health manpower training and the development and distribution of resources. It has not examined these problems and collected an appropriate data base of information such as any practicing physician would do in addressing a problem with a patient. Nor has it developed diagnosis and treatment plans in collaboration with others involved as would be the case with a problem in direct patient care. In short, and surprisingly enough, it never really has applied its own highly developed problem solving techniques to its own problems. And this has not been good either for medicine or for the public it serves.

But it is not yet too late. The problem solving techniques of medicine are uniquely adapted to changing situations, and changing situations will be characteristic of the foreseeable future of health, well-being, personal fulfillment and quality of life for America—and for the world. Perhaps a beginning has been made with the approach to tort reform in California. This was and is a social, economic and political problem. The chief complaint, soaring professional liability insurance rates, was obvious enough, and after some to-do, the true nature and scope of the problem was identified by the House of Delegates of the California Medical Association as a social, economic and political ailment of modern American society, and not just of medicine and lawyers. The unprecedented step was taken of creating an independent commission on tort reform within which medicine, in collaboration with many others who are involved, could work to gather a data base, to refine the diagnosis and to prescribe a treatment program. The treatment, it is hoped, will match the dimensions of the problem, and have a broad enough base of support so that the ailment can be managed in a rational way which will lead to an eventual cure.

Rapid change will be a hallmark of third century America. We must learn to deal with this effectively within a framework of increasing interdependence, which will be another hallmark of the coming century. Medicine has much to offer the nation if it can begin to adapt its biological knowledge and its problem solving skills not only to the changing needs of patient care, but also to some of the changing social, economic and political problems of assuring health, well-being and quality of life for all the people.

—MSMW

Cell-Mediated Immunity — Resistance to Infection and So Much More

RECOGNITION of the participation of leukocytes, particularly phagocytic cells, in the host defense against infection has long antedated our understanding of the concept of specific immunity mediated by lymphoid cells against infectious agents. In turn, appreciation of cell-mediated immunity specifically directed against various microorganisms has led to greater insight into the potential and real importance that immunity mediated by cells holds in other diverse areas of human biology and clinical medicine.

In the current issue of the WESTERN JOURNAL Wing and Remington have clearly and succinctly outlined the diverse mechanisms and manifestations of immunity against a variety of microorganisms that are mediated directly or indirectly by thymus-derived (T) lymphocytes. Although many phases of the afferent as well as the efferent limb of the immune response are dependent on the participation of leukocytes of various classes, the term cell-mediated immunity is generally reserved for those processes under the direction of, or actually mediated by T cells. Yet, it is now becoming quite clear that such sharp dichotomies between different types of immune responses may not be entirely appropriate, given the cooperation and regulatory processes existing between lymphocyte subpopulations in the development of an effective immune response.[1,2]

In any event, evidence is now quite firm that cell-mediated immunity plays an important role in the manner in which the human host handles infection from a variety of organisms including several bacteria, fungi, viruses and parasites. Its importance to the survival of the host is clear. However, it has also become obvious over recent years that the infectious disease model of cell-mediated immunity has crossed the boundaries of most of the other subdivisions of clinical medicine and now forms the basis of our understanding of the pathophysiology of such diverse phenomena as immune rejection of tumor, autoimmune disease, rejection of allografts and the graft-versus-host reaction among others. The con-

cept that forms the common denominator of cell-mediated immunity against infectious microorganisms and these other phenomena is that of "foreignness." In its most uncomplicated form, the rejection of foreignness constitutes the basis of the cellular immune response to most of the classic infections which are handled in this manner. Under normal circumstances in an intact host, such rejection of foreignness proceeds in a relatively unnoticed manner virtually every day of our lives. When there are subtle alterations in the actual foreignness of the microorganism, an inability of the host to recognize foreignness, or a defect (naturally occurring or iatrogenically acquired) in the response to foreignness, compromise of the host ensues.

However, the efficiency and integrity of this surveillance process is indeed a double-edged sword. In most infectious diseases it clearly works for the protection of the host. However, this is not always the case. As Wing and Remington mention in this issue, two well studied viruses in mice illustrate this point. Ectromelia virus, the agent causing mousepox, which is a disease of mice similar to smallpox in humans, is controlled by a T cell-mediated lysis of virus-infected cells resulting in elimination of infection. On the other hand, lymphocytic choriomeningitis virus invades host cells and causes very little harm to the infected tissues. It is the activity of the T lymphocytes specifically sensitized to the virus-infected cells that causes tissue damage and is responsible for the deleterious effects of the disease. A somewhat analogous situation is seen in the immune response to neoplastic cells versus the immunological reactivity in autoimmune disease. An appropriate self-nonself recognition and response to neoplastic cells forms the basis of tumor surveillance and is to the advantage of the host. On the other hand, an aberration of this self-nonself recognition may lead to immune reactivity against normal host tissues and hence autoimune disease.

Further analogies can be drawn between the immune response to tumors and that directed against nematode parasites. It is well recognized that tumor rejection by the host's immune mechanisms can be impeded by various blocking factors as well as by tumor related immunosuppression. Likewise, interference with or blocking of the immune response is seen with the infection Nippostrongylus brasiliensis in rats and may explain the lack of an effective immune response against this and other parasites.[3]

One of the most important and exciting areas into which an appreciation of the complex mechanisms involved in the host response to infections has led is that of the genetics of the immune response. It has been recognized that different strains of mice of various histocompatibility types are either highly susceptible or resistant to various infections such as lymphocytic choriomeningitis virus[4] and leukemia virus-associated disease.[5] This is analogous to the varying abilities of mice of different histocompatibility types to mount a specific immune response to various antigens. Such control of specific immune responses has been shown to be linked to the major histocompatibility locus (H-2 locus) of the animal in question.[6] The link is through what is now known as a specific immune response (Ir) gene. Hence, the susceptibility to infection in certain strains of mice may be directly related to their ability or lack of ability to mount an effective immune response against the infectious agent. Indeed, presently available evidence points to a histocompatibility-linked Ir gene control of immune responses to certain viral antigens.[7] The potential implications of this are truly enormous, particularly in light of the familial pattern of certain diseases together with current hypotheses linking viral infections with certain neoplasms[8] as well as autoimmune disease.[9]

Hence, further appreciation of the complex factors underlying immune responses in infectious diseases of necessity will cross interdisciplinary boundaries and carry with it insight into other areas of clinical medicine.

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CASE REPORTS

Refer to: Bennett WM, Gilbert DN, Houghton D, et al: Gentamicin nephrotoxicity—Morphologic and pharmacologic features. West J Med 126:65-68, Jan 1977

Gentamicin Nephrotoxicity —Morphologic and Pharmacologic Features

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GENTAMICIN, an aminoglycoside antibiotic, is commonly prescribed for treatment of serious infections with Gram-negative bacteria. The drug is thought to be primarily excreted unchanged by glomerular filtration. Adjustment of dosage based on this measure is widely thought to avoid excessively high serum concentrations and thereby minimize extrarenal and renal toxicity.[1,2] Although human gentamicin nephrotoxicity has been reported, pathophysiologic data are limited because of the complex clinical circumstances in which the drug is administered.[3,4] In the Fisher 344 rat strain, given doses similar to those used clinically, proximal tubular cells undergo changes suggestive of cellular autophagy—such as numerous cytosegresomes with whorled inclusions probably of cell membrane origin.[5] Harrison and coworkers noted similar changes in Sprague-Dawley rats only with higher doses and attributed them to lysosomal injury.[6] Luft and associates have correlated these morphologic features in rats with accumulation of gentamicin in the renal cortex. They found a renal tissue half-life of 109 hours compared with a serum half-life of 35 minutes.[7] We report similar pathologic findings in a patient six weeks after a course of gentamicin therapy. Despite the long duration since therapy was discontinued low levels of gentamicin were detected in the renal cortex and urine implying significant tissue accumulation. This phenomenon would appear to be incompatible with renal gentamicin handling by glomerular filtration alone.

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Report of a Case

After 4,320 rads of preoperative irradiation in a 52-year-old woman with adenocarcinoma of the endometrium, radical hysterectomy was done with enflurane anesthesia on April 26, 1975. During operation the right ureter was transected and primarily repaired. The left ureter was injured also and reimplantation into the bladder was required. On the 12th postoperative day a temperature to 105°F developed and a left-sided pelvic abscess was drained with prompt defervescence. On May 21 fever returned. Both blood and urine cultures grew Pseudomonas aeruginosa sensitive *in vitro* to gentamicin. An intravenous pyelogram showed a normal right collecting system. The left ureter was duplicated with obstruction of the lower system at the ureterovesical junction. The patient was transferred to the University of Oregon Health Sciences Center, where a left nephrostomy was carried out under nitrous oxide anesthesia. Administration of gentamicin, 1 mg per kg of body weight given intramuscularly every eight hours, was begun. Before antibiotic therapy, laboratory studies gave the following values: hematocrit reading, 32 percent; blood urea nitrogen (BUN), 7 mg per 100 ml; creatinine, 1 mg per 100 ml, and creatinine clearance 96 ml per minute. The patient was 165 cm (5 ft 5 in) tall and weighed 79 kg (174 lb). No diuretics or other antibiotics were administered during her stay in hospital. The clinical course is detailed in Figure 1. The urine culture rapidly became sterile. However, in view of the documented bacteremia, a 14-day course of therapy was recommended. Because of deteriorating renal function, dosage was decreased despite appropriate peak and trough

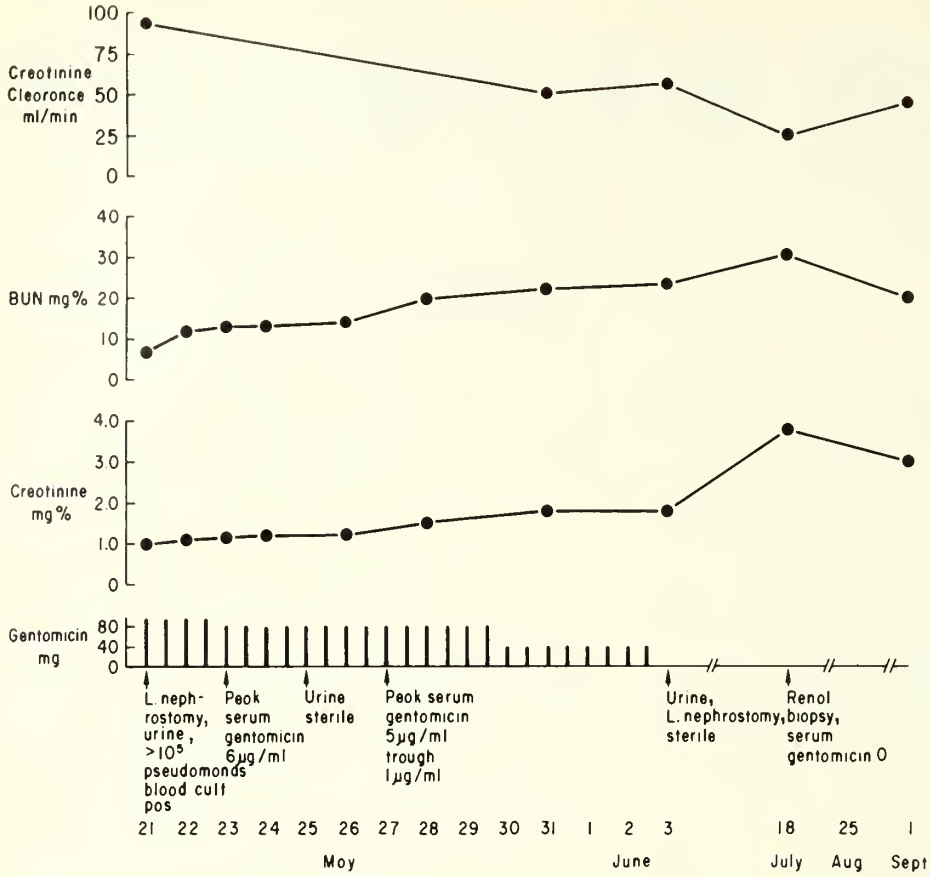

Figure 1.—Clinical course of the patient is shown. Progressive deterioration of renal function reached peak six weeks after last dose of gentamicin was given.

gentamicin serum levels on May 27. Total gentamicin dosage for the 14-day course was 1,840 mg with a maximum individual dose of 1.3 mg per kg of body weight. She was discharged on the 14th day and no medications were ordered.

When the patient presented for follow-up one month after discharge, she had complaint of fatigue, weight loss and weakness. Weight was 72 kg (158.7 lb). Findings on physical examination and vital signs were normal. Analysis of urine showed tubular epithelial cells, a pH of 6.0 and 10 to 15 leukocytes per high power field. Cultures from the left nephrostomy and urine were sterile. The protein level on a 24-hour urine study was 920 mg. The following values for electrolytes were noted: sodium, 142 mEq per liter; potassium 4.2 mEq per liter; chloride 113 mEq per liter; bicarbonate 18 mEq per liter. BUN was 36 mg per 100 ml, creatinine 3.7 mg per 100 ml and creatinine clearance 41 ml per minute. An intravenous pyelogram showed mild right-sided calyceal dilatation and a left nephrostogram showed no ureteral obstruction. On July 18, 1975, a right-sided open renal biopsy was done. Specimens of bladder urine, left nephrostomy urine and renal cortical tissue were analyzed for gentamicin by a modification of the radio-enzymatic assay of Smith and Smith.[8] Findings for renal cortical tissue showed a concentration of 30 μg per gram of wet tissue, while both urine samples showed 1.1 μg per ml. A serum gentamicin level obtained on the same day was 0.

Light microscopy showed normal glomeruli but significant swelling, vacuolization and necrosis of proximal and distal tubular cells. In addition interstitial fibrosis and tubular dilatation were prominent. On ultrastructural examination of tubular cells, myeloid bodies, numerous cytosegresomes and mitochondrial swelling were noted (Figures 2 and 3). There was no glomerular or tubular deposition of immunoglobulins or complement.

There was gradual improvement in renal function in the patient as assessed by BUN and creatinine values following volume repletion and bicarbonate therapy. At last observation creatinine clearance was 66 ml per minute.

Discussion

Gentamicin, a widely used aminoglycoside antibiotic with a serum half-life of two hours, has been reported to cause reversible renal failure in

man due to proximal tubular necrosis.[3,4] It has been difficult to ascertain the determinants of nephrotoxicity in man due to the serious underlying diseases for which the drug is prescribed. Gyselink and co-workers in studying the renal handling of gentamicin in man proposed almost complete quantitative excretion of administered drug by glomerular filtration.[1] If this is true significant drug accumulation and presumably nephrotoxicity should be minimized by adjusting the drug dosage to the glomerular filtration rate in a patient.[2] Recent morphologic observations by Kosek and associates in rats showed proximal tubular cell ultrastructural lesions in animals without renal failure given as little as 1 mg per kg of body weight of gentamicin per day.[5] Renal cortical tissue uptake has been confirmed by Luft and co-workers in rats given single doses of gentamicin.[7] These authors reported a renal cortical half-life of 109 hours with a serum half-life of 35 minutes. Kalmeter and Kamme detected gentamicin in the urine of a patient a month after treatment.[9] Alfthan and co-workers have shown renal concentrations 20 times that of serum in renal tissue of patients with normal renal function treated with single doses of gentamicin before urologic operations were carried out.[10] The present case provides direct evidence in a patient of ultrastructural lesions similar to those described in rats and documents evidence of tissue accumulation six weeks after therapy was discontinued. Wellwood found similar proximal tubular changes on electron microscopy in three renal allograft recipients receiving administration of gentamicin. Details of dosage and serum gentamicin levels, however, were not specified.[11]

It is of note that the drug was not given in excessive dosage nor did the peak serum levels one hour after a dose or trough levels directly before a dose exceed the recommended values.[12] It is possible that previous radiation therapy, urosepsis or urinary tract obstruction predisposed to nephrotoxicity. The lack of pathologic evidence for such processes plus the normal creatinine clearance measured before therapy make these possibilities unlikely. It has been reported that furosemide,[13] cephalosporins,[14,15] and methoxyflurane potentiate aminoglycoside nephrotoxicity;[16] however, none of these agents were given to our patient. Enflurane, the anesthetic administered during original surgical procedure in the patient, has been reported rarely to cause nonoliguric acute renal failure;[17,18] however, renal function was clearly normal up to one month following anesthesia.

The exact determinants of the tissue gentamicin

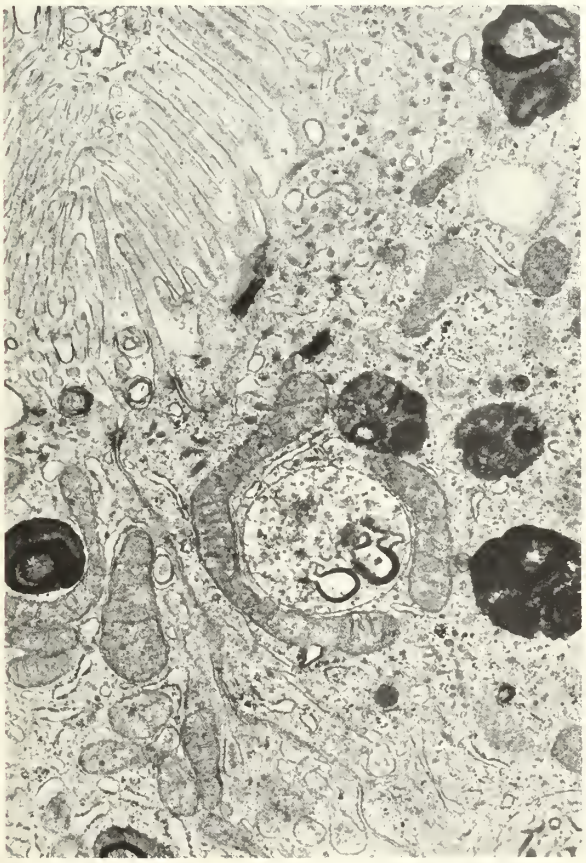

Figure 2.—A proximal tubule cell with numerous lysosomes containing dark granular debris and myeloid bodies. There is focal swelling of the endoplasmic reticulum. There are several myeloid bodies in the intervillous spaces. (upper left) 24,000x

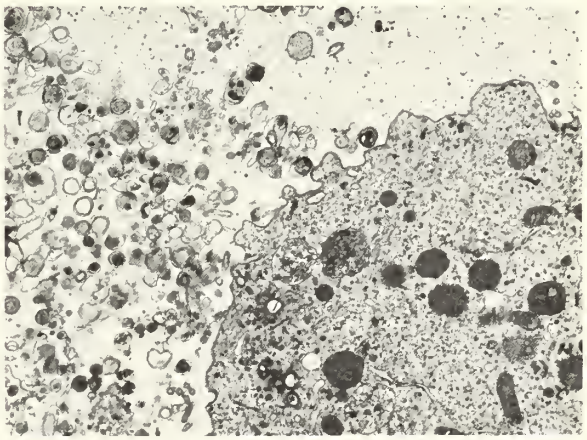

Figure 3.—A distal convoluted tubule cell and lumen filled with cytoplasmic debris and numerous unicentric myeloid bodies. The cell contains numerous lysosomes and a few small mitochondria. 24,000x

accumulation in our patient and its relation to deterioration of function remains speculative. Nonetheless, detection of nephrotoxicity by monitoring BUN and creatinine levels as customarily carried out may be too insensitive to detect early signs of tubular damage. Luft and co-workers have found in rats that lysosomal enzymuria and proteinuria are early indicators of nephron dysfunction.[19] Similar observations have been reported by Wellwood and associates in renal transplant patients.[11] It is clear from the present report that current dosage recommendations will not always insure freedom from nephrotoxicity.

Summary

Partially reversible nonoliguric renal failure developed in a patient while gentamicin therapy was being carried out. Dosage was monitored by peak and trough serum gentamicin levels and serum values never exceeded 6 μg per ml and 1 μg per ml, respectively. Six weeks after therapy was discontinued a renal biopsy study showed proximal tubular necrosis with numerous cytosegresomes, myeloid bodies and mitochondrial swelling on electron microscopy. Similar lesions have been recently reported in experimental aminoglycoside nephrotoxicity in rats. At the time of renal biopsy the renal cortical gentamicin concentration was 30 μg per gram of wet tissue, the serum gentamicin value was 0 and the urine gentamicin value was 1.1 μg per ml. It is concluded that gentamicin can cause proximal tubular lesions in man similar to those described in rats. The significant renal tissue uptake of the drug that occurs may have pathophysiologic significance in nephrotoxicity.

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Medicine and the Quality of Life

QUALITY OF LIFE increasingly is being identified as a goal of medicine and health care. In the July issue, the editors began a forum for discussing the actual and ideal relationships between medicine and the quality of life by printing seven articles expressing differing views. The following comments were generated by those articles and ones in succeeding issues.

Readers are invited to take part in a continuation of this forum by submitting their comments, written as succinctly as possible. As many of these as space permits will be published in future issues. At an appropriate time all the material will be collated and, if possible, the distillate will be prepared as a statement to summarize the dialogue that has taken place.

Reverence for Life

BERNARD L. TUCKER, MD, Los Angeles

MEDICINE CAN IMPROVE the quality of life through reverence for life. We need constant reaffirmation of our purpose to treat the sick and injured by our willingness to serve, to show compassion and to help.

Reverence for life, an integral if sometimes neglected part of our medical tradition, is aptly expressed by Dr. Albert Schweitzer: "The man who has become a thinking being feels a compulsion to give to every will-to-live the same reverence for life that he gives to his own. He experiences that other life in his own. He accepts as being good: to preserve life, to promote life, to raise to its highest value life which is capable of development; and as being evil: to destroy life, to injure life, to repress life which is capable of development."

The world we live in becomes more mechanical and less humane with each passing day, and the practice of medicine has not been spared from these changes. The technologic progress in medicine has been so rapid and important that we, and perhaps through us, our patients and society as a whole, have emphasized the science of medicine instead of stressing its humaneness. Seemingly these advances in medicine have outpaced our ability to handle the resulting new conditions. As never before we seem beset with problems that repeatedly assail our ears, preoccupy our minds and trouble our hearts. The malpractice predicament, with the numerous suits and threat of countersuits, demonstrates how malevolent the doctor-patient relationship can be. The role of peer review and quality assurance in the delivery of medical care is unsettled. Various solutions have been proposed for these and other perplexing problems.

It is not enough to be efficient, self-reliant and independent; to have all the qualities needed to organize, to act and to command. We must guard against being more at ease with manuscripts, instruments and interesting cases than with a person distressed and in need of compassion.

In a world seemingly more harsh, kindness is not always respected, is often misunderstood and is too frequently submerged in a mounting concern for efficiency. Worthy of emulation is the physician who is able to dispense large doses of warmth and goodness in every encounter with patients and colleagues. Even today, when we experience scientific sophistication in medicine as never before, there still is much room for compassion and a real void without it.

Men and women, through their reason and will, take their place in society and conduct themselves according to its standards. As physicians, we should consciously uphold the truth and that which is right even when current norms might dictate otherwise. With the ever increasing role of government in medicine, there is justified concern that patients will become lost in the bureaucracy of the system and that medical care will be seriously lacking in individuality and humaneness.

Reverence for life should be manifested in every aspect of our being, our appearance and our deportment, and should be extended to all including the unborn, the physically and mentally infirm, the sick, the aged and the dying. Our real purpose, reflecting the spirit of the evangelist Luke and countless others after him, should be a warm, healing relationship with our patients and fellow men. Indeed, this reverence for all life is the only reliable foundation upon which the true quality of life can be elevated.

Refer to: Tucker BL: Reverence for life, *In* Medicine and the quality of life—A forum. West J Med 126:69, Jan 1977

Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgment before publication.

Benefits and Risks of Screening Mammography

To THE EDITOR: Breslow's critique [Breslow L: Radiation risks of mammography—Another view (Editorial Comment). West J Med 125:495-497, Dec 1976] of my editorial [Sickles EA: Radiation risks of mammography (Editorial). West J Med 125:493-495, Dec 1976] makes three major points. (1) He admits that there is no hard evidence of breast cancer induction by mammography as it is practiced today and apparently recognizes the fact that informed scientific opinion is just about equally divided for and against the linear extrapolation and no threshold hypotheses. Armed with this information he concludes that the "prudent" approach is to assume an unspecified but finite oncogenic risk, even though this risk may be immeasurably small. (2) He chooses to limit acceptable evidence of the benefits of mammography to the HIP [Health Insurance Plan of Greater New York] study,[1] since this is the only *controlled* study so far published which directly indicates data on patient survival. (The HIP study found that screening mammography significantly prolonged survival but that its beneficial effects were limited to women age 50 and above). (3) From these points he concludes that screening mammography is inadvisable for women under 50, because of a finite risk and no proved benefit.

This simple and cogent analysis would seem to have considerable merit, except for one fatal flaw: point (2) is incorrect, and therefore point (3) does not logically follow.

It is as clear to me as it is to every other working mammographer that the practice of mammography is currently far more advanced than it was as done by the HIP radiologists in 1963. Evidence of this abounds; the largest and therefore most meaningful experience is that of the Breast Cancer Detection Demonstration Project (BCDDP). One *can* derive much valuable information from these data, even though there is no matched control group. For example, the rate of detection of clinically occult cancer (cancer found by mammography but missed on physical examination) in the BCDDP is substantially higher than that of the HIP study (46 percent versus 19 percent of all cancers discovered by screening).[2] Furthermore, this interval improvement in yield applies almost equally to women under and above age 50. Lundgren, in screening the entire female population over age 35 of a Swedish community, showed even higher yields for mammography.[3] I interpret these findings as indicating a definite interval improvement in the ability of mammography to detect clinically occult cancer, for women both under and above age 50.

To disregard this evidence totally (I cite only the tip of the iceberg) and demand instead a randomized clinical trial is hardly "prudent." Rather, it is shortsighted and I believe unwise. Although a randomized clinical trial is the best way to demonstrate the efficacy of a diagnostic modality, it is not the only way, especially if the diagnostic modality is as accurate and productive as mammography. Would it really be "prudent" to ask 50 percent of the women in a clinical trial to wait until their breast cancers become palpable before receiving treatment when we know that in about half of them a cancer will be discovered earlier with the addition of screening mammography? I think not, especially since we also know that clinically occult cancers are associated with a much lower incidence of positive axillary nodes than palpable cancers, and that the presence of positive axillary nodes is an indicator of increased morbidity and mortality.

Even granting Breslow's "prudent" approach to the potential risks of mammography (that is, assuming that there are risks, although these may indeed be minimal or nonexistent), recognition of the recent advances in mammography and the implied benefits to women both under and over

age 50 prompts a completely different solution to the question of whether screening mammography should be done in women 35 to 50 years old. Rather than halting such screening and placing the burden of proof on mammographers to justify the success of their technique with a randomized clinical trial, I propose to continue reaping the benefits of screening and place the burden of proof on radiobiologists to *unequivocally* define and quantitate the risks. Mammography has been done for well over 20 years, and for the first 15 years at radiation doses 25 to 50 times greater than now possible. Yet I am not aware of, and I challenge Breslow to produce, even one proved case of breast cancer resulting from mammography. When dealing with a cancer detection technique even more accurate than the Pap smear, it is inconceivable to abandon that technique on the basis of unproved risk.

Mammography is indeed one of the triumphs of modern radiology. To attempt to discredit it on the basis of insufficient evidence of risk and to also ignore the great majority of evidence demonstrating its utility is overly cautious, misleading and incorrect. I again urge that screening mammography of women age 35 to 50 be continued in the BCDDP.

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1. Strax P: Control of breast cancer through mass screening. JAMA 235:1600-1602, Apr 12, 1976
2. Preliminary (current) statistics. Breast Cancer Detection Demonstration Project, Bethesda, MD, Jul 19, 1976
3. Lundgren B, Jakobsson S: Single view mammography—A simple and efficient approach to breast cancer screening. Cancer 38:1124-1129, 1976

Preventive Medicine and Behavior Change

TO THE EDITOR: Congratulations to Dr. Breitman for his clear, good sense letter in the September 1976 issue [Breitman G: Preventive medicine—A myth. West J Med 125:236, Sep 1976], from one who is actually in the field and not in the dream world.

It occurs to me that perhaps public misunderstanding (intentionally or unintentionally promoted) is due to misuse of the term "preventive medicine." The public may rightfully associate preventive medicine with the great advances in public health due to the work of physicians and medical scientists which controlled the great epidemic and infectious diseases. In that situation the physician was actually able to provide the drug or immunization or sanitation or other factor which resulted in the longevity and freedom from disease we all enjoy. That is real "preventive medicine."

But the "preventive medicine" that the sociologists and politicians are referring to should better be called "behavioral change medicine." The difference is fundamental because the result in this situation isn't ultimately under the control of the physician but depends on the actions of the patient, the public; depends on a change in long-established habits, personalities, environments and a myriad of other factors over which the physician has *no* control.

Our medical-social organizations in dealing with the promotors of this fallacy should insist on a stricter definition. The planners' grand proposal ought be called by something other than the honored term "preventive medicine."

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Physician's Assistants in California

TO THE EDITOR: In the December issue was a letter [Reade FZ: More on physician's assistants. West J Med 125:498, Dec 1976] by Frank Z. Reade, MD, regarding physician's assistants (PA) misrepresenting themselves as physicians.

I appreciate the concern expressed by Dr. Reade regarding an incident where a physician's assistant identified himself as a physician during a telephone conversation. In no way will an attempt be made to justify the action of any person, PA or not, who intentionally misrepresents himself as a physician.

A physician's assistant is a particularly vulnerable professional—we represent a new and basically unknown concept to the general public. A patient automatically assumes that anyone in a white jacket who does the work of a physician must indeed be a physician, thus he calls this practitioner "doctor" out of respect and tradition. Certainly, to encourage this facade is wrong, but to advocate that every time a PA is called a "doctor" that he immediately retorts with a lengthy dissertation of the role and evolution of midlevel health practitioners is equally unjustified. The classic "What's a PA?" bombards us daily and sometimes we have a tendency not to overempha-

size that we are not physicians in order to spare this repetitive, time-consuming lecture. This is neither wrong nor deceptive. No physician's assistant should have to introduce himself with "Hi . . . I'm not a doctor . . . now what seems to be the problem," but under *no* circumstances can a PA refer to himself as "doctor."

Similar in nature is a psychologist without a doctorate who goes by "doctor," which traditionally implies "physician," and a nurse's aide in a hospital who answers to the word "nurse" when she is neither a registered nurse nor a licensed vocational nurse. It is also a common practice in medical schools to refer to medical students as "doctors" when indeed they are years away from receiving their degree. The Physician's Assistant Examining Committee has gone to extraordinary lengths to prevent this very problem for physician's assistants. At present, to conform with the law patients are required to sign an "informed consent" stating they acknowledge that "A Physician's Assistant will be rendering certain medical services under the supervision of the primary care physician." And if that isn't sufficient to eliminate misrepresentation, we are also required to wear an identifying badge stating our name and "Primary Care Physician's Assistant." Even with all these safeguards, nothing short of a neon sign will prevent an occasional ego from promoting itself. The PA in question is obviously not proud to be a PA and is suffering from an inferiority complex that he is not a physician. This is more his personal problem and stems from not accepting what he is. I believe that this incident was an exception, rather than the rule. To state that all PA's misrepresent themselves as physicians is a blanket implication without substantiation, and we who are ethical resent that.

And now a word about supervision. PA's are *dependent* practitioners and are trained to extend the services of a primary care physician like a "right hand," and the body should always be aware of what that right hand is doing. Under California law, the supervising physician, according to Article 15, Section 1379.22 (amended October 28, 1976) states that "the physician has the continuing responsibility to follow the progress of the patient and to make sure that the Physician's Assistant does not function autonomously." A supervising physician who doesn't regulate the actions of the PA in his practice should not have a PA. The "buck" stops at the physician.

The PA concept works, but only if both the PA and the physician know their abilities and limitations and properly establish themselves as a team. Most midlevel health practitioners (physician's assistants, nurse-practitioners and so forth) are acutely aware of their roles, their limitations and their ability to function as "assistants."

Traditionally, only physicians in the United States could carry out medical skills. Recognizing that physicians need help in the performance of those duties led to the development of a second profession, nursing. The roles of physicians and nurses tended to be sharply defined. A nurse was prohibited from doing even routine tasks which by law were exclusively in the province of a trained physician. It has only been recently that sources of untapped medical skills have been utilized, and PA's and nurse practitioners evolved and began to make an impact on the chronic shortage and misallocation of primary medical care.

Large numbers of Americans still go without good medical care and not necessarily in medically underserved areas. Physician's assistants may be part of the answer, but certainly not part of the question.

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Refer to: Billstein S: School-based immunization clinics—A method for raising community immunization levels (Public Health). West J Med 126:73-78, Jan 1977

School-Based Immunization Clinics

A Method for Raising Community Immunization Levels

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A survey in ten Sacramento schools indicated that immunization levels were low and that they compared with the low levels estimated by the Center for Disease Control for the rest of the country. The problem was given priority, and a plan evolved using the community's schools.

A method was developed to screen and immunize large numbers of children in a short time. The schools were used as a focal point to immunize both school-aged and preschool-aged children in each section of Sacramento County. A trained immunization team carried out immunizations with high cost effectiveness.

IN THE PAST, public health departments used community schools in mass immunization campaigns. The schools served as a focal point for immunizing school-aged children, pre-schoolers and adults whenever mass campaigns were launched with the development of a new vaccine. The last school program in Sacramento County, California, took place in 1969 when live rubella vaccine was offered to the public. Since 1969, immunizing children to diphtheria, tetanus, pertussis, polio and rubeola has continued to be a part of all county public health programs. In Sacramento County, the onus for getting children immunized was shifted to the parents who either opted to immunize their children (private medical sector or public health well-baby clinics) or not to immunize their children.

From the Department of Community Health, Sacramento County Health Agency, Sacramento.

Reprint requests to: Stephan Billstein, MD, MPH, Assistant Director, Department of Community Health, Sacramento County Health Agency, 3701 Branch Center Road, Sacramento, CA 95827.

Background

Current legislation in the State of California[1] requires children upon admission to school to be adequately immunized against rubeola, polio, and diphtheria, pertussis and tetanus (DPT). Current guidelines recommend that the child have a rubeola immunization at age 1 or older; polio immunizations (trivalent) at 2 months, 4 months and 6 months (or 2, 3 and 4 months) of age, with boosters at age 18 months, and at age of school admission; and DPT immunizations at the same times that polio immunization is given with an additional diphtheria and tetanus (DT) immunization every ten years following the last booster.[2]

Despite the legislative mandate and publicity by public health organizations, medical societies and paramedical professional associations, herd immunization levels in children are low. Center for Disease Control (CDC) statistics (1973)[3-5] indicate that among 1- to 4-year-old children in

ABBREVIATIONS USED IN TEXT

CDC = Center for Disease Control
DPT = diphtheria, pertussis and tetanus
DT = diphtheria and tetanus

the United States, 39 percent remain unimmunized against rubeola, 40 percent remain unimmunized against polio and 27 percent remain unimmunized against diphtheria, pertussis and tetanus.

In March 1972 local Community Health Department workers in Sacramento County (population approximately 670,000) began to look at immunization levels in county children 14 years old and younger to determine if they were comparable to the CDC national estimates. The Sacramento City Unified School District was chosen for sampling because it was the only public school district in the county that had its health data on a computer system. By surveying ten elementary schools in this district, it became apparent that Sacramento's immunization levels were low and compared with the CDC's low national estimates. The sampling indicated that 33 percent of the children were inadequately immunized to diphtheria, pertussis, tetanus and polio, and that 50 percent of the children were not immunized to rubeola.

At that time the public health department was giving immunizations free at well-baby clinics throughout the county, and at four permanent health centers. The onus was on the parent to seek out the public health clinic for immunizations. Little outreach activity was practiced. It was realized that a more aggressive approach toward raising immunization levels was needed.

Plan of Action

A plan evolved that set as its goal raising the immunization levels in Sacramento County's 14-year-old and under population to greater than 95 percent immunized within three years. Clinics would be run in elementary schools throughout the county for school and preschool children offering free rubeola, rubella, polio, DT and DPT immunizations.

During the first school year of operation (1973-1974), the Health Agency conducted approximately two school clinics per week. Of approximately 186,000 children, 14 years old and younger in Sacramento County, 21,465 were screened in 34 school clinics. A total of 21,837 immunizations was given to 10,005 children (Table 1).

In 1974-1975, school clinics were increased to 10 to 12 per week, and as a result 72,123 children were screened in 169 school clinics with a total of 66,467 immunizations being given to 31,032 children (Table 1).

Costs and Effectiveness

The cost effectiveness of the fiscal year 1974-1975 immunization program can be seen in Table 2. The cost per child screened was $1.93, and of children actually immunized, $4.54 per child.

During the fiscal year 1973-1974 immunization program (Table 3) the cost per child screened was $2.26, and of children actually immunized, $4.86 per child.

The normal cost to private physicians for individual unit doses of the vaccines alone is $0.32 for DPT; $0.20 for DT; $3.47 for measles/rubella; $2.25 for measles; $5.85 for measles/mumps/rubella, and $0.75 for polio. These costs plus the charge for the patient visit to a private physician's office would be considerably more than the cost per child calculated for this program.

During the first six months of 1975, Sacramento County had an outbreak of rubeola with 310 cases reported in that period (January 1 through June 30). The last peak year was 1972, when a total of 141 cases was reported during the calendar year.

When the 310 cases of rubeola were analyzed as to age of child afflicted, there were 17 children age 4 and under, 93 children between ages 5 and 9, and 200 children 10 and over. It would appear that the immunization program had been effective in the program's target group (preschool and elementary school children).

Most of the cases of rubeola occurred in junior and senior high school students, 200 out of 310 cases or 64 percent. Investigating 25 of these cases with histories, physical examinations and serologic titers proved that the students indeed did have rubeola despite a school health record indicating previous immunization with live vaccine. However, all of these immunizations occurred between 1963 and 1968, and were either administered before age 1 or given with immune serum globulin, or both. None of these children had been revaccinated.

A rescreening of the elementary schools in the 1975-1976 school year where clinics had been held in the previous two school years showed that

newly entering students (kindergarten and some first grade children) needed the most immunizations. The children who had had previous immunization screening and been through immunization clinics needed less. Statistics were gathered to show totals for each school only, and indicated that on the average 10 percent of children needed rubeola immunization, about 33 percent needed polio, DT or DPT boosters, and less than 1 percent needed primary immunizations to polio, DPT or DT.

TABLE I.—*School Clinic Immunizations—Sacramento County 1973-74, 1974-75*

	School Year 1973-74	*School Year 1974-75*	*Percent Increase*
Total children screened	21,465	72,123	336
Total children immunized	10,005	31,032	310
Total DPT given	1,275	2,725	214
Total DT given	7,349	23,018	313
Total polio given	8,231	28,080	341
Total MR given	4,932	12,354	250
Total immunizations given	21,837	66,467	304

DPT = diphtheria, pertussis and tetanus
DT = diphtheria and tetanus
MR = measles/rubella

TABLE 2.—*Costs of Immunization Program for Fiscal Year 1974-75 (School-Based Clinics Only)*

	Number Given	*Cost*
Immunizations		
DPT	3,204	$ 1,025.28
DT	23,721	4,744.20
Measles/rubella	12,810	44,450.70
Measles	305	686.25
Measles/mumps/rubella	62	362.70
Polio	29,442	22,081.50
Total		73,350.63
Personnel		
Nursing time		46,817.71
Physician time		4,130.00
Clerk time		17,401.30
Total		68,349.01
Supplies		
Purchase of 3 immunization guns		2,655.00
Printing, promotion, mailing		1,000.00
Travel mileage		1,600.00
Telephone		500.00
Miscellaneous nursing supply		200.00
Total		5,955.00
Grand Total		$147,654.64

	Number	*Cost/Child*
Children immunized	32,552	$ 4.54
Children screened	76,561	$ 1.93

DPT = diphtheria, pertussis and tetanus
DT = diphtheria and tetanus

Method

The method used consisted of five parts; planning, screening, immunizing, recording, and follow-up.

Planning

During the planning phase school officials are contacted, the need for immunization is explained to them and their cooperation is requested. Meetings are then held to orient school district nurses and school principals as to immunization needs and the operation of the clinics in their schools. At these meetings, the dates are set for actual immunization clinics.

Screening

Screening sheets (see Figure 1) are given to the school at least two weeks in advance of the clinic. Teachers are informed by the school nurses and principals about the importance of students taking the screening sheets home to their parents and having the sheets completed and returned. The immunization clinic dates are well publicized in the local neighborhood news media, among

TABLE 3.—*Costs of Immunization Program for Fiscal Year 1973-74 (School-Base Clinics Only)*

	Number Given	*Cost*
Immunizations		
DPT	1,275	$ 408.00
DT	7,349	1,469.80
Measles/Rubella	4,932	17,114.04
Polio	8,231	6,173.25
Total		25,165.09
Personnel		
Nursing time		10,221.97
Physician time		4,130.00
Clerk time		7,272.38
Total		21,624.35
Supplies		
Use of 3 immunization guns (borrowed from state)		no charge
Printing, promotion, mailing		1,000.00
Travel mileage		252.80
Telephone		500.00
Miscellaneous nursing supply		65.80
Total		1,818.10
Grand Total		$ 48,608.04

	Number	*Cost/Child*
Children immunized	10,005	$ 4.86
Children screened	21,465	$ 22.6

DPT = diphtheria, pertussis and tetanus
DT = diphtheria and tetanus

STATE DEPARTMENT OF HEALTH - SACRAMENTO COUNTY HEALTH AGENCY

Dear Parent:

A free Immunization Clinic will be held on

ALL children (age 2 months & older) can be immunized free. Each child MUST have a signed permission form. Extra permission forms for younger children will be available at the school. Infants under 12 months of age who have not started their immunizations must have a statement from their physician that they may be immunized.

FEMALES OVER 12 YEARS OF AGE WILL NOT BE GIVEN RUBELLA (3 DAY MEASLES) VACCINE.

IT IS RECOMMENDED THAT CHILDREN WHO RECEIVED 7 DAY MEASLES (RUBEOLA) VACCINE PRIOR TO 1968 BE RE-IMMUNIZED BECAUSE THEY MAY NOT BE ADEQUATELY PROTECTED.

If you have questions or cannot attend this clinic phone 440-7200 regarding other immunization clinics held throughout the County.

PLEASE FILL OUT AND RETURN THIS FORM TO YOUR CHILD'S TEACHER BY TOMORROW. RETURN THIS FORM EVEN IF YOUR CHILD WILL NOT GET IMMUNIZED.

A nurse will determine what immunizations your child needs BASED ON THE INFORMATION YOU GIVE US. A slip indicating which immunizations were received will be given to each child to be taken home to update their personal immunization records.

Child's name_____ Age____ Grade____ Teacher_____

IMMUNIZATION HISTORY

DOES YOUR CHILD have a serious or chronic illness?	☐ YES	☐ NO	If yes, please explain on back.
HAS YOUR CHILD ever had a serious reaction to immunizations previously received [high fever (102 degrees or greater), convulsions, etc.]?	☐ YES	☐ NO	If yes, please explain on back.
IS YOUR CHILD ALLERGIC TO: ☐ Eggs ☐ Feathers ☐ Antibiotics?		☐ NO	If yes, please explain on back.
HAS your child been immunized against Rubella? (Commonly called German or 3 day Measles).	☐ YES	☐ NO	☐ DON'T KNOW
YEAR RECEIVED _____			☐ DON'T KNOW
Has your child ever been sick with Rubella? (Commonly called German or 3 day Measles).	☐ YES	☐ NO	☐ DON'T KNOW
HAS your child been immunized against Rubeola? (Commonly called 7 day or Hard Measles).	☐ YES	☐ NO	☐ DON'T KNOW
YEAR RECEIVED _____			☐ DON'T KNOW
Has your child ever been sick with Rubeola? (Commonly called 7 day or Hard Measles).	☐ YES	☐ NO	☐ DON'T KNOW
CIRCLE the number of oral Polio doses your child has had:	0 1 2 3 4 5		☐ DON'T KNOW
YEAR LAST DOSE RECEIVED _____			☐ DON'T KNOW
CIRCLE the number of Diphtheria, Pertussis, Tetanus, (DPT, or baby shots) your child has had:	0 1 2 3 4 5		☐ DON'T KNOW
YEAR LAST SHOT RECEIVED _____			☐ DON'T KNOW

GIVE MY CHILD THE NEEDED IMMUNIZATIONS . . . . . ☐ YES ☐ NO

Date_____ Signed_____ Phone No._____

FOR OFFICIAL USE ONLY IZ's given: ☐ DPT ☐ POLIO ☐ MEASLES ☐ DT ☐ MR

revised 1/6/76 rm

FIGURE 1.—Immunization sheet for school.

local neighborhood organizations, and on television in order to attract preschool children. The screening sheets are distributed. They have been designed to bring the children's school medical records up to date, to determine needed immunizations and to record the immunizations given.

Upon return of the screening sheets, all parent referrals are separated out and are noted. Those sheets without a parental signature are checked on by either PTA volunteers or by the school nurse.

Following the actual clinic, the screening sheet is affixed to the children's permanent school health records.

Immunizing

The officials of each school are asked to provide four volunteer helpers and a room for the clinic with separate entrance and exit doors, two tables and an adequate number of chairs. The Department of Community Health is responsible for giving the immunizations. The service is delivered by a team consisting of a clerk, a registered nurse or public health nurse, nurse-immunizers and school volunteers. Their duties are as follows:

- *Clerk.* (1) Records the number of children given immunizations and the kind(s) of immunization(s) given. (2) Hands to each child color-coded "immunization-give" tickets so that parents can enter necessary information in the child's immunization record.
- *Registered Nurse (RN)* or *Public Health Nurse (PHN) (Reviewer.)* (1) Reviews all screening sheets carried by children. The teachers hand the screening sheet back to the child just before the clinic. The children give the screening sheet to the reviewer who determines if child and screening sheet match (name and age); and what immunizations the child needs. The imunizations given are then noted on the bottom line of the screening sheets (see Figure 1). (2) Instructs the clerk to hand the children the color-coded "immunization-give" tickets. These tickets are coded, with white for DPT, yellow for DT, red for rubeola/rubella and green for polio. The tickets are dated and given to the children who are instructed to give them to their parents (updates children's records).
- *Nurse-immunizers* (can be licensed vocational nurse (LVN), RN or PHN)—two are necessary. (1) They receive the color-coded tickets from the children and immunize either by gun (Ped-o-jet), or by syringe and needle depending on clinic volume. (2) They are experienced in handling immunization reactions.
- *School Volunteers*—four are needed. One volunteer keeps the children in an orderly line, and instructs them to roll up their sleeves. Another writes the child's name on the "immunization-give" tickets. A third rubs the acetone on the child's arm before immunization. A fourth helps to hold the children who resist.

Recording

The team clerk is responsible for determining the number of children screened before the clinic, the number of children actually receiving immunizations at the clinic and the number of immunizations given at the clinic, correlated as to type of immunization and age. The school nurses are responsible for updating the children's school immunization records by placing the completed screening sheet in their health folders.

Follow-up

Schools will be offered immunization clinic sessions approximately every three years. During the interim, a public health aide will be assigned to screen the immunization records of all new school enterers once a year. The aide will note the number of children inadequately immunized and a report will be made to the school principal following the aide's visits.

Untoward Reactions

During school years 1973-1974 and 1974-1975, immunization clinics were held in a total of 203 Sacramento County schools in which 88,304 immunizations were given to 41,037 children. Six reports of inflamed injection sites following measles/rubella immunization were reported. All of these children responded to symptomatic therapy (aspirin, local compresses and arm rest). In no children was clinical rubeola known to have developed following a clinic. In one child the eruption of rubella developed within 30 minutes of immunization. This was felt to be street virus infection. Ten children were reported as having local reactions following DPT or DT immunization. These reactions consisted of one or more of the following: erythema, edema, axillary lymphadenopathy, malaise, temperature elevation ($<100°F$), anorexia and headache.

All responded to symptomatic therapy. In one child, age 6, with a history of four previous injections for DPT a nephrotic syndrome was re-

ported to have developed within two days of receiving the immunization. Investigation showed that this child had a history of growth retardation, and several developmental disabilities. It was felt that the nephrotic syndrome was not a result of the immunization that he received at the clinic. No diarrhea or other complications were attributed to the polio immunizations.

Conclusion

It has been shown in Sacramento County, California, that a county-wide school-based immunization program is an effective way of raising community immunization levels. The program enables children to be immunized at no additional direct cost to the parents (because it is funded by tax money). It also enables schools to update records of the children's immunization status and, it is to be hoped, prevents outbreaks of formerly epidemic diseases (and attendant student absences).

It is usually difficult to evaluate the decreased incidence of diseases that were formerly epidemic in such a short time when general population herd immunity is allegedly high. However, the year 1975 afforded the opportunity to show that during a community rubeola outbreak, the incidence of the disease was low in the population affected by the school immunization clinics, whereas in the junior and senior high school children, the measles case rate was high.

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2. Report of the Committee on Infectious Diseases 1974, American Academy of Pediatrics

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4. Center for Disease Control, Rubella, Measles, Polio Immunization Status Report No. 20, Jun 1973

5. Summary of Immunization Status for Polio, DPT, Measles, and Rubella, United States, 1974. U.S. Immunization Survey, 1974

Insulin Versus Orally Given Hypoglycemic Drugs in the Treatment of Diabetes

Insulin may be preferable to the use of orally given hypoglycemic drugs in patients in whom normoglycemia is not achieved. . . . An obese patient with diabetes who, on diet, is unable to have reasonable normoglycemic levels and who is symptomatic should certainly have some medication to lower blood glucose levels. My feeling is that in these patients insulin can accomplish the objective, although some of them may already have an increased amount of insulin in their bodies. But we have seen these patients respond to insulin administration with normoglycemia and a disappearance of symptoms.

—STANLEY N. COHEN, MD, *Philadelphia*
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Refer to: Lewis CE, Freeman H: The opinions and actions of physicians during a malpractice insurance crisis. West J Med 126:79-83, Jan 1977

Special Article

The Opinions and Actions of Physicians During a Malpractice Insurance Crisis

CHARLES E. LEWIS, MD, *and* HOWARD FREEMAN, PhD, *Los Angeles*

THE TERM "CRISIS" is used frequently in discussions of health care in the United States. Fortunately, the labeling of all problems in the medical care sector as crises represents an exaggeration. Most are either crises in the eyes of the beholders, or represent acute reactions to the discovery of long-term chronic problems. Early 1976, however, was at the very least "a crucial time" for the medical profession in California and for the state as a whole as a result of a sizable increase in the premiums for malpractice insurance.

This "malpractice insurance crisis," like most others, had been brewing for many years. In fact, a similar acute episode of lesser magnitude occurred in 1975 when large premium increases were threatened. Mobilization of physicians to fight rising insurance costs was stifled in 1975 by political-legislative actions that provided short-term, symptomatic relief.

Late in 1975, however, physicians were notified by the various insurance carriers that either they would no longer be able to provide malpractice coverage, or that they would increase premiums. In the face of either cancellations or sharp increases in the costs of coverage, individually and collectively physicians undertook a variety of actions to cope with the problem. Some of these were on the drawing boards since 1975. Petitions were circulated, committees were formed and political action groups were organized; in brief, the malpractice problem became a highly visible public issue. Despite these activities, there was no change in the position of the insurance carriers, and it became evident that January 1976 would bring a significant increase in the cost of coverage to practitioners throughout California.

As this deadline approached, there was a pronounced acceleration and intensification of the behavioral manifestations of concern by the medical profession. In addition to the somewhat benign activities of petition-signing and making statements to the press, actual closing of practices occurred, with a reduction in the volume of physicians' services available. The number of elective surgical procedures carried out, for example, dropped off to a notable degree (according to surveys conducted from December 1975 through February 1976 by *The Los Angeles Times).*

As evidence of an impending shortage of patient-care services increased, we decided to identify systematically the opinions held and the activities undertaken in response to the "malpractice insurance crisis" by practicing physicians in Los Angeles County. This study was timed so that interviews with physicians would cluster around the deadline for the payment of new premiums (January 28, 1976). In this paper, we present a summary of the results of the survey.

Dr. Lewis is Professor of Medicine and Head of the Division of General Internal Medicine and Health Services Research, Department of Medicine, and Dr. Freeman is Professor of Sociology and Director of the Institute of Social Science Research Departments of Medicine and Sociology, University of California, Los Angeles.

Supported in part by the UCLA Health Services Research Center Grant HS-02015.

Reprint requests to: Charles E. Lewis, MD, Department of Medicine, Health Services Research Center, UCLA Center for the Health Sciences, Los Angeles, CA 90024.

The Study Group

A random sample of 499 practicing physicians in Los Angeles County was drawn from the 1975-1976 directory of the Los Angeles County Medical Association. Table 1 lists the percentage of the practitioners by specialty included in the sample, compared with their relative distribution in the population of physicians within the county.

Letters were mailed to these physicians in advance to provide opportunity for informed consent when they were contacted. Telephone interviews were scheduled to span the period from January 25 to February 29, 1976. These were conducted by staff at the Survey Research Center of the Institute for Social Science Research, University of California, Los Angeles.

Of the 499 physicians in the sample, 12 percent (62) were no longer in practice at the time of the first telephone call. Except for three who had moved from the county, the rest had retired, or had discontinued their telephone service. Of the remaining 437, 68 percent (296) participated in the survey. Both the reasonably high response rate and the interest in the subject matter during the interview are indicators of the saliency of the subject to Los Angeles County doctors. In fact, some physicians who received letters describing the study called the Survey Research Center on their own initiative to make appointments for interviews.

Of the physicians from whom information was collected, slightly more than a fourth (26 percent) were interviewed before the deadline for paying the premium. There is no evidence of significant differences in the backgrounds of physicians or the information obtained from them among those interviewed before or after the deadline. Of the respondents, 93 percent were men. The median age was 51 years, 84 percent were white and the sample was geographically distributed, representing 118 zip code areas in the county.

Half of the study group had been in practice 20 years; 63 percent were board certified and 20 percent were board eligible. About 56 percent of the practitioners were in solo practice, 15 per-

TABLE 1.—*Specialty of Physicians Sample and County Distribution by Percent**

Specialty	*Sample N=296*	*Los Angeles County N=11,032*
General Practice	24.0	21.7
Internal Medicine/Cardiology	16.2	19.7
Surgery/Urology/Orthopedics/ Ophthalmology	23.3	19.5
Pediatrics	5.1	6.5
Obstetrics/Gynecology	8.4	7.3
Psychiatry	5.1	8.8
Radiology	3.7	5.0
Anesthesiology	4.7	4.4
Dermatology/Ear/Nose/Throat	4.1	3.6
Other	5.4	3.5

*County of Los Angeles Department of Health Services Planning and Budgeting Data Book, 1975.

TABLE 2.—*Actions Personally Participated in During the Crises by Age**

	PERCENT ACTIVE				
Type of Action	*30-39 N=32*	*40-49 N=95*	*50-59 N=96*	*60+ N=73*	*Total N=296*
Slowdowns	56.2	42.1	57.2	41.1	48.6
Letter Writing	62.5	51.5	55.2	43.8	52.4
Signed Petitions	62.5	53.6	68.7	47.9	58.4
Joined Committees and Groups	28.1	38.9	32.3	15.0	29.7

*Percentages total to more than 100 percent due to multiple responses.

TABLE 3.—*Plans for Future Practice*

Action	*Percent*
Practice as usual	51.5
Restrict practice	37.5
Stop practice completely	3.7
Increase fees	3.3
Stop until action taken	2.0
Move from California	1.0
Take a position where someone else pays for coverage	1.0

TABLE 4.—*Insurance Coverage and Practice Plans*

	INSURANCE COVERAGE (Percent)	
Practice Plans	*Plan to Carry in 1976 N=81*	*Not plan to carry in 1976 N=41*
Stop practice	9.9	19.5
Move practice	3.7	7.3
Restrict practice	86.4	73.2

TABLE 5.—*Plan to Carry Malpractice Insurance in 1976 by Specialty*

Specialty	*N=277*	*Percent who do not plan to carry malpractice insurance in 1976*
General Practice	67	26.9
Internal Medicine/Cardiology	46	10.9
Surgery/Urology/Orthopedics/ Ophthalmology/Neurology	61	37.7
Pediatrics	15	13.3
Obstetrics/Gynecology	23	52.2
Psychiatry	15	6.7
Radiology	11	18.2
Anesthesiology	12	33.3
Dermatology/Ear/Nose/Throat	11	27.3
Other	16	18.8

cent belonged to partnerships and 13 percent were practicing members of specialty groups. The median number of patients seen by these physicians was 85 per week, and one of eight patients seen was a Medi-Cal beneficiary. Only 10 percent of the physicians interviewed did not see Medi-Cal recipients. Some 25 percent of the patients of practitioners in this study were over 65 years of age.

Impact of Rate Increase

While more than 96 percent of the physicians were covered in 1975, only about 70 percent planned coverage for 1976 (all of this group reported they had paid the new premium at the time of the survey). This is reasonably similar to estimates that 75 to 80 percent of physicians had arranged coverage as reported in surveys conducted by the *Los Angeles Times* (February 4 and 5, 1976). Another 5 to 6 percent were undecided about coverage at the time of the survey. For the group who took out insurance, the median costs rose from $3,600 in 1975 to $8,000 in 1976.

Although most practitioners acquiesced and paid the much higher premiums, the typical physician in the county was an active opponent to the increase in premiums. Approximately half of the doctors were participants in slow-downs, letter writing and petition-signing and about a third joined one of several action groups formed in the county and state. As shown in Table 2, with the exception of joining such groups, a rarer action for practitioners over 60 years of age, there was participation by all age groups in actions opposing the increase. Moreover, neither years of practice, specialty nor other professional characteristics, including income, were systematically related to standing up to the carriers. Clearly the opposition was not limited to the younger generation.

The increased premiums affected practitioners' future plans. As shown in Table 3, only slightly more than half of the study group planned to practice as usual; more than a third intended to restrict practice by diagnosis, services provided or social characteristics of patients. If plans were realized, and the practitioners who planned to stop practice completely or move from the state actually took these actions, Los Angeles County will have had 5 percent fewer physicians in 1976 than in 1975.

As shown in Table 4, among the physicians who planned to change their practice as a response to the crisis, those taking the decisive actions of either stopping practice or moving were most likely to plan to not renew insurance. Some who planned to be insured are also in these categories, perhaps as a temporary protection until they make their long-term plans.

There were systematic differences by specialty regarding plans to carry insurance in 1976. As shown in Table 5, physicians who are either general surgeons or in practicing specialties such as obstetrics and gynecology, urology, ophthalmology and orthopedics were least likely to contemplate insurance coverage. In contrast, radiologists, internists and cardiologists more often paid the increased premiums.

There were also some differences in the social characteristics of insured and uninsured doctors, at least as they report about their plans. Plans to

TABLE 6.—*Perceived Impact of Crisis by Specialty on Income, Office Management, Public Opinion of Physician and Expected Morbidity*

		PERCENT REPORTING			
Specialty	*N**	*Some or great effect on income*	*Some or great effect on office management*	*Some or great effect on public opinion of physician*	*Expected increased morbidity*
General Practice	68	83.6	57.3	59.7	27.9
Internal Medicine/Cardiology	48	83.3	50.0	68.1	22.2
Surgery/Urology/Orthopedics/ Ophthalmology/Neurology	68	78.2	50.0	59.7	20.6
Pediatrics	15	57.1	6.7	53.8	7.7
Obstetrics/Gynecology	25	88.0	70.8	66.6	12.0
Psychiatry	15	50.0	33.3	80.0	40.0
Radiology	11	90.9	70.0	88.9	36.4
Anesthesiology	14	78.6	50.0	83.3	28.6
Dermatology/Ear/Nose/Throat	12	83.3	58.3	66.6	33.3
Other	16	80.0	21.4	62.6	25.0

*The sample numbers varied slightly from variable to variable because of occasional missing data.

practice "uncovered" were most common among those in the 40 to 49 age group and of physicians with incomes of less than $50,000 per year.

Opinions on Crisis

The physicians interviewed were asked to project the consequences of the insurance crisis on their income, the management of their office, and the public. As shown in Table 6, they clearly saw the increased premiums as affecting their incomes, with some 80 percent reporting negative impact. A large proportion, consistent with the finding that many doctors would restrict their practices, reported that the ways they managed their offices would be modified. Moreover, more than 70 percent felt it would have at least some impact on the public's conception of the medical practitioner, and many believed it would increase morbidity. These data are shown by practice specialty, with most of the differences explainable by the type of practice of physicians in the study group.

The survey also included items on who was to blame for the higher premiums and how to deal with the rising insurance costs (see Tables 7 and 8). The diagnosis and prescription are consistent: lawyers and the legal system were indicted most frequently. Almost half would restrict lawyers' fees in malpractice cases; more than a fourth would eliminate jury trials. Only one of eight believed improved doctor-patient relations would make a difference and less than 4 percent thought stricter peer review procedures were a remedy.

In view of the fact that a good deal of action on the legislative front had been concerned with the creation of doctor-controlled insurance carriers, it was of interest that only 2.4 percent believed that this was the most effective way of dealing with this dilemma. Doctors feel the malpractice crisis is exogenous to the medical care system and that the cure lies outside it as well.

TABLE 7.—*Responsibility for the Higher Insurance Premiums**

Groups Blamed	*Percent Believing Responsible N = 296*
Lawyers	82.1
Insurance companies	53.0
Public	34.8
Government	29.7
Some other group	20.9
Doctors	20.3
No one to blame	1.4

*Percentages total to more than 100 percent due to multiple responses.

TABLE 8.—*Ways to Reduce Fees*

Ways to Reduce Rates	*Percent Believing Most Effective N = 296*
Restrict lawyer fees	46.6
Eliminate jury trials	27.4
Improve impersonal relations	12.2
More peer review	3.7
Physician control insurance	2.4
Real informed consent	0.7
Stricter regulations	0.7

Discussion

As of the summer of 1976, the crisis seemed to have subsided—the problem once again became subclinical. A significant proportion of physicians, however, apparently, have elected not to carry malpractice insurance. Those "uncovered" are overrepresented by younger physicians in early and less remunerative stages of their practice careers, and those who are at high risk and have substantial premiums to pay. Some physicians, perhaps as many as 5 percent of the county's practitioners, may no longer be providing direct care services (this is currently being examined by our staff).

The data on the study group—age, sex, nature of practice, types of patients—are reasonably consistent with the general data on physicians in this area, suggesting that the sample was fairly representative of practicing physicians as a group. The opinions held by these physicians about the causes of the problems and the proposed treatment are consistent with most statements by physicians that have appeared in the press and news media.

Although the size of the sample and the information at hand do not allow for a full unraveling of the determinants of electing coverage, physicians were faced with the decision of could they or would they pay the increased costs of coverage. For some, personal opposition to the imposed increase and its perceived implications may have been the principal determinant. For others, the question was undoubtedly whether or not they could afford their premiums. Some who felt they could not increase their gross income —because of their length of time in practice, their specialty or the ability of their patients to pay increased fees—may have been unable, if not unwilling, to pay the insurance premiums.

For physicians in certain specialties, the sheer amount of the insurance may have been the key factor in not electing coverage. For some,

the premium approaches $40,000 per year, and a personal illness of one month would cause severe financial problems for a person in solo practice whose other expenses would continue during such an illness. Also, for some physicians in "high-risk" specialties, the combination of reducing total liability by having minimum assets in his or her own name that can be garnered in case of a large judgment, and a "self-insurance" investment program may seem to be a better option than the high premiums. Both practice and social characteristics of physicians in relation to their decision to elect insurance is an area that merits further study.

Summary

The chronic malpractice insurance crisis in California, indeed in the United States, has not been resolved. In this state, it has temporarily regressed to a tolerable level for physicians. As costs continue to escalate, and in all probability they will, by the next anniversary for payment of premiums the phenomenon may once again be repeated. In view of the notorious lack of efficacy of most of the actions taken in 1976, it will be of interest to examine future activities of physicians to see if actions of a different nature are advocated.

While malpractice is certainly affected by certain legal practices, many see it occurring as a result of a complex interplay of factors involving public expectations and physician negligence as well as the tort system. Concern with the physician's role in the malpractice insurance crisis was noticeably absent from the responses of those in the survey. While some acknowledged that public expectations of cure without consequences contribute to this problem, few advocated interventions based on dealing with patients *and* physicians in treating this systematic disorder that threatens the health of the health care system in the United States.

A New Approach to Episiotomies

Most of our episiotomies today are done in the midline. If you would like to extend your episiotomy, but feel that you've gone as far as you dare vaginally and do not wish to incise the rectal sphincter . . . put a bleb of novocain at about 2 o'clock and about 10 o'clock in the hymenal ring. Make small incisions in the hymen (they do not have to extend more than approximately one centimeter) and you will be surprised at the increase in the circumference that occurs at the hymenal margin which, in turn, will benefit you insofar as being able to deliver the child without incurring a laceration or an extension of the episiotomy.

—J. BROOKS HOFFMAN, MD, *Greenwich, CT*
Extracted from *Audio-Digest Obstetrics and Gynecology*, Vol. 23, No. 12 in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1930 Wilshire Blvd., Suite 700, Los Angeles, CA 90057.

Medical Practice Questions

EDITOR'S NOTE: *From time to time medical practice questions of general interest are referred to the Scientific Board by the Peer Review Commission of the California Medical Association. Each is sent to members of the appropriate Scientific Advisory Panel.* Their responses are collated, reviewed and then submitted to the Peer Review Commission as the Scientific Board's opinion on the scientific and practice aspects of the question. The Commission adds suggestions to assist peer review units and authorizes publication.*

These opinions and positions are informational only and are not intended to be used as instructions, directives or policy statements. The appropriateness of care in individual cases should not be determined by these answers, but should be reviewed by local peer review committees.

Questions and reprint requests may be submitted to the Medical Practice Questions Committee, Peer Review Commission, California Medical Association, 731 Market Street, San Francisco, CA 94103.

Irradiation of Plantar Warts

QUESTION:

Is radiation therapy accepted medical treatment for plantar warts? (Asked by the Fresno County Medical Society)

OPINION:

In the opinion of the Advisory Panels on Dermatology and Radiology, radiation therapy is accepted medical practice for treating plantar warts but its use should be limited to cases which have not responded to other forms of treatment.

Vitamin B_{12} for Hypoglycemia

QUESTION:

Are vitamin B_{12} injections acceptable medical practice for treating hypoglycemia? (Asked by San Bernardino County Medical Society)

OPINION:

In the opinion of the Advisory Panel on Internal Medicine, the use of vitamin B_{12} injections is not accepted medical practice for the treatment of hypoglycemia.

Gamma Globulin for Herpes Zoster

QUESTION:

Are injections of gamma globulin in the treatment of herpes zoster accepted medical practice? (Asked by Pacific Intermountain Express Co.)

OPINION:

In the opinion of the Advisory Panels on Dermatology and Internal Medicine, gamma globulin injections would not usually be considered acceptable treatment for herpes zoster, although there might be circumstances in which their use is reasonable (for example, severe herpes zoster in an immunologically incompetent patient).

Prosthetic Implants for Urinary Incontinence

QUESTION:

What types of prosthetic implants are used in the treatment of urinary incontinence? Please list the indications for use of each type. Which types are considered medically acceptable and which experimental? (Asked by H. Dean Hoskins, MD, State Department of Health)

OPINION:

In the opinion of the Advisory Panel on Urology, the Kaufman prosthesis and the Brantley Scott inflatable prosthesis are both implants accepted in the treatment of urinary incontinence.

The Kaufman prosthesis is the most commonly used one, primarily for postprostatectomy incontinence. Use of the Scott prosthesis is more limited; physicians using it must have special training. The Scott prosthesis is also used for postprostatectomy incontinence, but its principal use is in patients with incontinence due to neurogenic bladder decompensation.

Another type of implant, the acrylic Berry prosthesis, had poor results and is no longer in use.

*The Scientific Board of the California Medical Association has a Scientific Advisory Panel for each of 23 recognized specialties of medical practice. Each Advisory Panel includes representation from the appropriate department of each of the eight medical schools in California, representatives of specialty societies in the field and representatives from the Specialty Sections of the Association. The Advisory Panels are thus broadly and authoritatively based in both academia and practice.

in memoriam

Ambler, Alfred Carleton, Pasadena. Died September 10, 1976, aged 78. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1927. Licensed in California in 1927. Dr. Ambler was a member of the Los Angeles County Medical Association.

Berliner, Bernhard, San Francisco. Died November 26, 1976 in San Francisco, aged 91. Graduate of Albert-Ludwigs-Universität Medizinische Fakultät, Freiburg, Germany, 1909. Licensed in California in 1937. Dr. Berliner was a member of the San Francisco Medical Society.

Betts, James V., Palo Alto. Died September 25, 1976 in Santa Cruz of heart disease, aged 60. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1948. Licensed in California in 1948. Dr. Betts was a member of the Santa Clara County Medical Society.

Bratrud, Theodor E., Huntington Beach. Died October 15, 1976 in Phoenix, aged 60. Graduate of Marquette University School of Medicine, Milwaukee, 1940. Licensed in California in 1954. Dr. Bratrud was an associate member of the Los Angeles County Medical Association.

Brown, Gordon A., Los Gatos. Died October 16, 1976 in San Jose of heart disease, aged 64. Graduate of the University of Minnesota Medical School, Minneapolis, 1941. Licensed in California in 1947. Dr. Brown was a retired member of the Santa Clara County Medical Society.

Catton, Joseph, San Francisco. Died September 19, 1976 at Stanford Medical Center of heart disease, aged 86. Graduate of the University of California Medical School, Berkeley-San Francisco, 1913. Licensed in California in 1913. Dr. Catton was a retired member of the San Francisco Medical Society.

Chiapella, Karl Joseph, Chico. Died November 15, 1976, aged 63. Graduate of McGill University Faculty of Medicine, Montreal, 1939. Licensed in California in 1939. Dr. Chiapella was a member of the Butte-Glenn Medical Society.

Cox, Ronald Kitt, Mountain View. Died October 27, 1976 in Mountain View of cancer, aged 45. Graduate of the University of Southern California School of Medicine, Los Angeles, 1960. Licensed in California in 1961. Dr. Cox was a member of the Santa Clara County Medical Society.

Dingman, Lynn W., Chester. Died October 10, 1976 of heart disease, aged 46. Graduate of Kansas City College of Osteopathy and Surgery, Kansas City, MO, 1957. Licensed in California in 1958. MD degree from California College of Medicine, 1962. Dr. Dingman was a member of the Lassen-Plumas-Modoc-Sierra County Medical Society.

Donahue, James Patrick, Berkeley. Died October 4, 1976, aged 46, from gunshot wounds by assailants. Graduate of St. Louis University School of Medicine, 1956. Licensed in California in 1957. Dr. Donahue was a member of the Alameda-Contra Costa Medical Association.

Due, Floyd O., El Cerrito. Died November 11, 1976 in Berkeley of heart disease, aged 65. Graduate of the University of California Medical School, Berkeley-San Francisco, 1939. Licensed in California in 1939. Dr. Due was a member of the Alameda-Contra Costa Medical Association.

Eloesser, Leo K., San Francisco. Died October 4, 1976 in Tacambaro, Mexico, aged 95. Graduate of Medizinische Fakultät der Universität, Heidelberg, 1907. Licensed in California in 1909. Dr. Eloesser was a retired member of the San Francisco Medical Society.

Fabian, John Paul, Chico. Died October 30, 1976 in Chico of heart disease, aged 72. Graduate of Jefferson Medical College of Thomas Jefferson University, Philadelphia, 1930. Licensed in California in 1931. Dr. Fabian was a retired member of the Butte-Glenn Medical Society.

Fernandez, David J., Fresno. Died November 1, 1976 in Fresno of injuries received in automobile accident, aged 33. Graduate of Georgetown University School of Medicine, Washington, DC, 1969. Licensed in California in 1970. Dr. Fernandez was an affiliate member of the Fresno-Madera Medical Society.

Fiorica, Anthony, Concord. Died October 17, 1976 in Livermore of heart disease, aged 58. Graduate of the Chicago Medical School, 1950. Licensed in California in 1952. Dr. Fiorica was a member of the Alameda-Contra Costa Medical Association.

Frieseke, Oliver C., jr., Delano. Died in October 1976 at Stinson Beach of myocardial infarction, aged 45. Graduate of the University of Tennessee College of Medicine, Memphis, 1957. Licensed in California in 1961. Dr. Frieseke was a member of the Kern County Medical Society.

Greene, Armin B., San Francisco. Died March 29, 1976 of myocardial infarction, aged 44. Graduate of Northwestern University Medical School, Chicago, 1955. Licensed in California in 1956. Dr. Greene was an associate member of the San Francisco Medical Society.

Hogan, Michael J., San Francisco. Died November 6, 1976 in Mill Valley, aged 69. Graduate of Cornell University Medical College, New York, 1932. Licensed in California in 1935. Dr. Hogan was a member of the San Francisco Medical Society.

HUMPHREYS, JASPER MCADORY, Chico. Died October 4, 1976 in Chico of heart disease, aged 75. Graduate of the University of California Medical School, Berkeley-San Francisco, 1930. Licensed in California in 1930. Dr. Humphreys was a retired member of the Butte-Glenn Medical Society.

LANGSTON, MANLY, JR., San Francisco. Died November 8, 1976 in San Francisco of Hodgkin's disease, aged 37. Graduate of the University of Tennessee College of Medicine, Memphis, 1964. Licensed in California in 1968. Dr. Langston was a member of the San Francisco Medical Society.

LEWIS, RUBIN M., Berkeley. Died October 2, 1976 in Berkeley of pneumonia, aged 77. Graduate of the University of Pennsylvania School of Medicine, Philadelphia, 1930. Licensed in California in 1951. Dr. Lewis was a retired member of the Alameda-Contra Costa Medical Association.

LYONS, THOMAS G., Stockton. Died October 31, 1976 in Stockton of heart disease, aged 56. Graduate of Tulane University School of Medicine, New Orleans, 1946. Licensed in California in 1946. Dr. Lyons was a member of the San Joaquin County Medical Society.

MORGAN, JOHN TRAMBLE, Norwalk. Died September 26, 1976, aged 58. Graduate of the University of Louisville School of Medicine, 1951. Licensed in California in 1952. Dr. Morgan was a member of the Los Angeles County Medical Association.

MUSANTE, ATTILIO S., San Francisco. Died November 16, 1976 in Redwood City, aged 94. Graduate of Cooper Medical College, San Francisco, 1907. Licensed in California in 1907. Dr. Musante was a retired member of the San Francisco Medical Society.

OSTWALD, EUGEN, San Francisco. Died November 25, 1976 in San Francisco, aged 81. Graduate of Martin Luther Universität Medizinische Fakultät, Halle-Wittenberg, Prussia, 1920. Licensed in California in 1937. Dr. Ostwald was a member of the San Francisco Medical Society.

PLUMMER, GEORGE W., Burlingame. Died October 24, 1976 in Burlingame, aged 53. Graduate of the University of Rochester School of Medicine & Dentistry, 1947. Licensed in California in 1954. Dr. Plummer was a member of the San Mateo County Medical Society.

PROTAS, EDWIN SHELDON, San Diego. Died April 18, 1976 of generalized lymphosarcoma, aged 37. Graduate of the University of Miami School of Medicine, Coral Gables, 1965. Licensed in California in 1970. Dr. Protas was a member of the San Diego County Medical Society.

REA, WALTON J., Ukiah. Died March 11, 1976 of bronchogenic carcinoma, aged 62. Graduate of McGill University Faculty of Medicine, Montreal, 1942. Licensed in California in 1943. Dr. Rea was a member of the Mendocino-Lake County Medical Society.

STANLEY, LEO L., Fairfax. Died November 13, 1976 at his home near Fairfax, aged 90. Graduate of Cooper Medical College, San Francisco, 1912. Licensed in California in 1912. Dr. Stanley was a retired member of the Marin Medical Society.

THOMPSON, ARTHUR RALPH, Berkeley. Died November 1, 1976 in Walnut Creek of bronchopneumonia and cerebrovascular accident, aged 75. Graduate of the University of California Medical School, Berkeley-San Francisco, 1927. Licensed in California in 1927. Dr. Thompson was a retired member of the Alameda-Contra Costa Medical Association.

THORNBURG, FRANK MILLER, Castro Valley. Died October 8, 1976 in Castro Valley of carcinoma of the lung, aged 60. Graduate of Indiana University School of Medicine, Bloomington-Indianapolis, 1944. Licensed in California in 1944. Dr. Thornburg was a member of the Alameda-Contra Costa Medical Association.

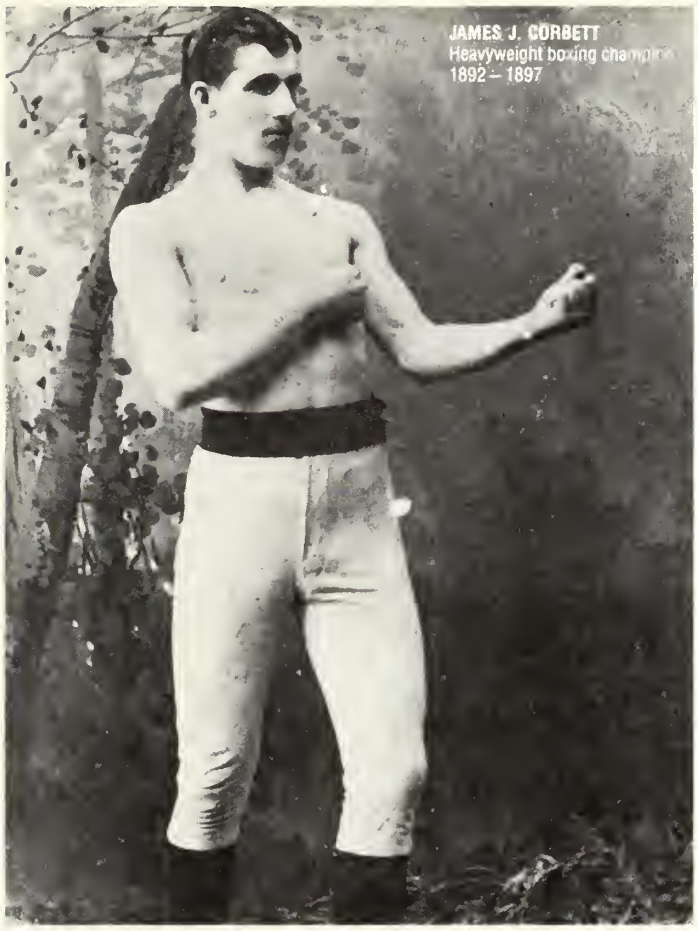
TOOHEY, JOHN JOSEPH, Ventura. Died September 18, 1976, aged 52. Graduate of the University of Wisconsin Medical School, Milwaukee, 1948. Licensed in California in 1953. Dr. Toohey was a member of the Ventura County Medical Society.

TURAIDS, OJARS, San Leandro. Died November 14, 1976 in the Virgin Islands of acute bacterial endocarditis, aged 44. Graduate of the University of California School of Medicine, San Francisco, 1962. Licensed in California in 1963. Dr. Turaids was a member of the Alameda-Contra Costa Medical Association.

VAJTA, PAUL, Los Altos Hills. Died February 5, 1976 of myocardial infarction, aged 78. Graduate of Deutsche Universität Medizinische Fakultät, Prague, 1923. Licensed in California in 1942. Dr. Vajta was a retired member of the Los Angeles County Medical Association.

YOUNGER, JESSE, Vallejo. Died November 25, 1976 in Kentfield of cancer, aged 56. Graduate of St. Louis University School of Medicine, 1945. Licensed in California in 1952. Dr. Younger was a member of the Solano County Medical Society.

Famous Fighters



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Provides overlapping, broad-spectrum antibacterial action to help combat infection caused by common susceptible pathogens (including staph and strep).

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INDICATIONS: Therapeutically (as an adjunct to systemic therapy when indicated) for topical infections, primary or secondary, due to susceptible organisms, as in: • infected burns, skin grafts, surgical incisions, otitis externa • primary pyodermas (impetigo, ecthyma, sycosis vulgaris, paronychia) • secondarily infected dermatoses (eczema, herpes, and seborrheic dermatitis) • traumatic lesions, inflamed or suppurating as a result of bacterial infection.

Prophylactically, the ointment may be used to prevent bacterial contamination in burns, skin grafts, incisions, and other clean lesions. For abrasions, minor cuts and wounds accidentally incurred, its use may prevent the development of infection and permit wound healing. **CONTRAINDICATIONS:** Not for use in the eyes or external ear canal if the eardrum is perforated. This product is contraindicated in those individuals who have shown hypersensitivity to any of the components. **WARNING.** Because of the potential hazard of nephrotoxicity and ototoxicity due to neomycin, care should be exercised when using this product in treating extensive burns, trophic ulceration and other extensive conditions where absorption of neomycin is possible. In burns where more than 20 percent of the body surface is affected, especially if the patient has impaired renal function or is receiving other aminoglycoside antibiotics concurrently, not more than one application a day is recommended. **PRECAUTIONS:** As with other antibacterial preparations, prolonged use may result in overgrowth of nonsusceptible organisms, including fungi. Appropriate measures should be taken if this occurs. **ADVERSE REACTIONS:** Neomycin is a not uncommon cutaneous sensitizer. Articles in the current literature indicate an increase in the prevalence of persons allergic to neomycin. Ototoxicity and nephrotoxicity have been reported (see Warning section).

Complete literature available on request from Professional Services Dept. PML.

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CANCER

January 24-28—**Cancer.** STAN. Monday-Friday. $250.

March 6—**Tumors of the Salivary Gland.** Calif. Tumor Tissue Registry at Disneyland Hotel, Anaheim. Sunday. 6 hrs. $100. Contact: Weldon K. Bullock, MD, Ex. Dir., Calif. Tumor Tissue Registry, 1200 N. State St., Los Angeles 90033. (213) 226-4614.

March 16-19—**Modern Concepts in Oncology—5th Annual Seminar.** UCLA at Beverly Hilton Hotel, Beverly Hills. Wednesday-Saturday.

March 19—**Cancer Screening and Cancer Control.** UCSF at Childrens Hospital, San Francisco. Saturday.

March 19—**Tumor Immunology, Clinical Applications.** San Francisco Regional Tumor Foundation at San Francisco. Saturday. Contact: Norma Schlager, PhD, S.F. Regional Tumor Foundation, 14th and Lake, San Francisco 94118. (415) 221-2132.

March 24-25—**Clinical Cancer Conference—11th Annual.** UCSF. Thursday-Friday.

March 25—**Cancer of the Ovary.** California Hospital Medical Center, Los Angeles. Friday. Contact: Kenneth L. Senter, MD, Dir., Med. Ed., CHMC, 1414 S. Hope St., Los Angeles 90015. (213) 748-2411.

MEDICINE

January 17-20—**Ischemic Heart Disease Problems and Perspectives.** Univ. of Hawaii School of Medicine, American Heart Assn., Hawaii Heart Assn. at Royal Lahaina Hotel, Maui, Hawaii. Monday-Thursday. 13 hrs. $175. Contact: Hawaii Conference Services, P.O. Box 22679, Honolulu 96822.

January 21-23—**Advances and Controversies in the Diagnosis and Management of Ischemic Heart Disease.** American College of Cardiology at Century Plaza Hotel, Los Angeles. Friday-Sunday. Contact: Mary Anne McInerny, Dir., Dept. of Cont. Ed. Programs, ACC, 9650 Rockville Pike, Bethesda, MD 20014.

January 22-23—**Dermatologic Surgery.** See Surgery, January 22-23.

January 23-29—**Topics in Internal Medicine—2nd Annual.** UCSD at Town and Country Hotel, San Diego. One week.

January 24-26—**Cardiac Auscultation.** American College of Physicians at LLU. Monday-Wednesday. 18 hrs. Contact: Registrar of Postgraduate Courses, ACP, 4200 Pine St., Philadelphia, PA 19104.

January 26-28—**Advances in Neurology.** UCSF at Mark Hopkins Hotel, San Francisco. Wednesday-Friday.

February 2-April—**Cardiology for the Practicing Internist.** UCLA. Wednesday evenings.

February 3—March 10—**Pulmonary Disease—7th Annual Postgraduate Course.** LLU. Tuesdays.

February 9—**Psychological Effects of Renal Dialysis.** See Psychiatry, February 9.

February 13-17—**Pulmonary Medicine.** UCSF at Lake Tahoe. Sunday-Thursday.

February 14-19—**Pediatric Nephrology and Urology.** See Pediatrics, February 14-19.

February 16-18—**Recent Advances in Gastroenterology.** UCSF at Fairmont Hotel, San Francisco. Wednesday-Friday.

February 18-19—**Dermatotoxicology.** UCSF. Friday-Saturday.

March 2-4—**Acute Respiratory Failure in Black and White—Annual Postgraduate Course.** California Thoracic Society at Sir Francis Drake Hotel, San Francisco. Wednesday-Friday. 18 hrs. $150 for members; $175, nonmembers. Contact: Ms. Elma Plappert, Exec. Sec., CTS, 424 Pendleton Way, Oakland 94621. (415) 638-5864.

March 11-12—**Clinical and Technical Application of the Intra-Aortic Balloon Pump.** See Surgery, March 11-12.

KEY TO ABBREVIATIONS AND SYMBOLS

Medical Centers and CMA Contacts for Information

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103. (415) 777-2000.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Duane Dillman, PhD, Director, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 564-5911, ext. 391.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr., MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, Ext. 2400.

PMC: Pacific Medical Center
Contact: Allen J. Enelow, MD, Chairman, Education Committee, Pacific Medical Center, P.O. Box 7999, San Francisco 94120. (415) 563-4321.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Neil C. Andrews, MD, Chairman, Department of Postgraduate Medicine, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, California College of Medicine, Irvine
Contact: Robert Combs, MD, Associate Dean, Continuing Medical Education, University of California, Irvine—California College of Medicine, Irvine 92717 (714) 833-5991.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, P.O. Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: David Allan, MD, Associate Dean for Continuing Medical Education, 1309 Basic Sciences Building, University of California, San Diego, School of Medicine, La Jolla 92037. (714) 452-3708.

UCSF: University of California, San Francisco
Contact: Malcolm S. M. Watts, MD, Associate Dean and Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 226-2047.

March 11-13—**American College of Physicians—Southern California Regional Meeting.** Vacation Village Hotel, San Diego. Friday-Sunday. Contact: John C. McCall, Jr., MD, 9844-400 Genesee Ave., La Jolla 92037.

March 12—**Echocardiography.** PMC. Saturday.

March 14-16—**Advances in Cardiology.** Foundation for Cardiovascular Research and Hospital of the Good Samaritan at Riviera Hotel, Palm Springs. Monday-Wednesday. 17½ hrs. $200. Contact: Foundation for Cardiovascular Research, 10 Congress St., Suite 203, Pasadena 91105.

March 15-16—**American College of Physicians—Hawaii Regional Meeting.** Pacific Club, Honolulu. Tuesday-Wednesday. Contact: Bernard W. D. Fong, MD, 97 Dowsett Ave., Honolulu 96817.

March 17-19—**Cardiovascular Disease—1977: Practical Diagnosis and Management.** American College of Cardiology at Hotel del Coronado, Coronado. Thursday-Saturday. Contact: Mary Anne McInerny, Dir., Dept. of Cont. Ed. Prog., ACC, 9650 Rockville Pike, Bethesda, Md. 20014.

March 18—**Practical Approach to Coagulation.** PMC. Friday.

March 21-25—**Arrhythmia Retreat.** USC at Erawan Garden Hotel, Palm Springs. Monday-Friday.

March 21-April 1—**Intensive Review of Internal Medicine.** USC. Two weeks.

March 24-25—**Cardiac Disease for the Practicing Physician, Diagnosis and Management 1977—3rd Annual Symposium.** Los Angeles Heart Institute at St. Vincent Medical Center, Los Angeles. Thursday-Friday. 10 hrs. $100. Contact: Irma Larsen, RN, L.A. Heart Institute, 123 S. Alvarado St., Los Angeles 90057. (213) 413-5220.

March 26—**Pulmonary Artery Catheters and Ventilators.** PMC. Saturday.

March 28-April 1—**Consultant's Course in Dermatology.** UCSF. Monday-Friday.

March 30—**Cardiac Care in Your Office.** American Heart Assn., Central Valley Chapter, at Sheraton Inn, Fresno. Wednesday. 6½ hrs. $35. Contact: Norman Sharrer, MD, 3835 N. West Ave., Fresno 93705.

April 4-13—**Cardiology for the Consultant: A Clinician's Retreat.** American College of Cardiology at Rancho Santa Fe. 10 days. Contact: Mary Ann McInerny, Dir., Dept. of Cont. Ed. Programs, ACC, 9650 Rockville Pike, Bethesda, MD 20014.

April 18-22—**Advances in Internal Medicine.** UCSF. Monday-Friday.

April 23—**Controversies in Internal Medicine.** The San Jose Hospital and Health Center, Inc., and San Jose Hospital Foundation at Marriott's Great America, Santa Clara. Saturday. 6 hrs. $25. Contact: Stanley Skillicorn, MD, Dir. of Med. Ed., The San Jose Hosp. and Health Ctr., Inc., 675 E. Santa Clara, San Jose 95112. (408) 998-3212.

April 28-30—**New Approaches to Cardiac Diagnosis.** PMC at Fairmont Hotel, San Francisco. Thursday-Saturday.

OBSTETRICS AND GYNECOLOGY

January 29-February 5—**Perinatal Medicine.** USC at Royal Lahaina Hotel, Maui, Hawaii. One week.

February 5-6—**Ob-Gyn Forum.** Los Angeles Obstetrical and Gynecological Society at Beverly Hilton Hotel, Beverly Hills. Saturday-Sunday. Contact: Miss Dee Davis, Exec. Sec., Los Angeles Obstetrical and Gynecological Society, 5410 Wilshire Blvd., Los Angeles 90036. (213) 937-5514.

February 5-7—**Comprehensive Laparoscopy.** UCSD. Saturday-Sunday.

February 7-11—**Obstetrical and Gynecological Assembly of Southern California.** Los Angeles Obstetrical and Gynecological Society at Beverly Hilton Hotel, Beverly Hills. Monday-Friday. Contact: Miss Dee Davis, Exec. Sec., Los Angeles Obstetrical and Gynecological Society, 5410 Wilshire Blvd., Los Angeles 90036. (213) 937-5514.

February 17-19—**Neonatology.** USC. Thursday-Saturday.

March 18—**Birth Defects, Genetics and the High Risk Patient.** UCD at Sacramento Inn, Sacramento. Friday.

March 18—**Diabetes in Pregnancy.** USC. Friday.

March 25-27—**Gynecological Urology.** USC at Marriott Hotel, Newport Beach. Friday-Sunday.

PEDIATRICS

January 22-23—**Pediatric Urologic Seminar.** Children's Hospital of Los Angeles. Saturday-Sunday. Contact: H. H. Edelbrock, MD, Program Dir., CHLA, P.O. Box 85544, Los Angeles 90027.

January 26—**Adolescent Medicine.** DREW at Martin Luther King Jr. Hospital, Los Angeles. Wednesday.

January 28-30—**Pediatric Anesthesiology.** See Surgery and Anesthesiology, January 28-30.

February 3-5—**Adolescent Medicine.** USC at Canyon Hotel, Palm Springs. Thursday-Saturday. 21 hrs.

February 14-19—**Pediatric Nephrology and Urology.** UCSD at Vacation Village, San Diego. Monday-Saturday.

February 24-26—**Clinical Problems in Pediatrics—Annual Winter Meeting.** Children's Hospital Medical Center of Northern Calif. at Sahara Tahoe Hotel, Lake Tahoe. Thursday-Saturday. Contact: Gretchen Hayes, CHMC, 51st and Grove Sts., Oakland 94609.

March 11-13—**Clinical Pediatrics.** American Academy of Pediatrics, Dist. IX, Chap. II; Childrens Hosp., of L.A.; L.A. Pediatric Society; Childrens Hosp. of Orange County; Southwestern Pediatric Society at Riviera Hotel, Palm Springs. Friday-Sunday. 12 hrs. $100. Contact: AAP, Dist. IX, Chap. II, P.O. Box 2134, Inglewood 90305.

March 25-26—**Infectious Diseases in Children.** UCD at Sacramento Inn, Sacramento, Friday-Saturday.

March 27-31—**Radiological Approach to Pediatric Problems.** See Radiology, March 27-31.

April 4-6—**American Association of Pediatric Ophthalmology.** PMC at Holiday Inn, Union Square, San Francisco. Monday-Wednesday.

April 15-16—**Aches, Pain and Dramatic Diseases in Children and Young Adults.** USC at Children's Hospital, Los Angeles. Friday-Saturday.

PSYCHIATRY

January 30-February 4—**Mid-Winter Program for Psychiatrists—3rd Annual.** UCD at Hyatt Lake Tahoe, Incline Village. Sunday-Friday.

February 5-6—**Clinical Hypnosis and Behavior Modification.** UCLA. Saturday-Sunday. 14½ hrs. $175.

February 9—**Psychological Effects of Renal Dialysis.** UCD at Sacramento Inn, Sacramento. Wednesday.

February 11-12—**Adolescence Today: Psychosocial Issues—3rd National Seminar.** Vista Hill Foundation and Sharp Memorial Hospital at Hotel del Coronado, Coronado. Friday-Saturday. 10 hrs. $65. Contact: Virginia Everett, Dir., Public Relations, Vista Hill Foundation, 7798 Starling Dr., San Diego 92123. (714) 278-6761.

April 2—**Evaluation and Management of Dangerous Behavior.** UCD at Sacramento Host, Sacramento. Saturday.

April 30-May 1—**Psychological and Medical Management of Stress.** UCLA at Santa Cruz. Saturday-Sunday.

RADIOLOGY AND PATHOLOGY

January 28-30—**Midwinter Radiological Conference—29th Annual.** Los Angeles Radiological Society at Century Plaza Hotel, Los Angeles. Friday-Sunday. Contact: Ronald W. Thompson, MD, Cedars-Sinai Medical Center, 4833 Fountain Ave., Los Angeles 90029.

January 28-30—**Radioimmunoassay Symposium.** UCSF. Friday-Sunday.

January 31-February 4—**Computerized Tomography.** UCSF at Fairmont Hotel, San Francisco. Monday-Friday.

February 2-4—**Genitourinary Pathology—4th Annual Course.** Memorial Hospital Medical Center, Long Beach. Wednesday-Friday. 20 hrs. $150. Contact: Margaret Frederick, Exec. Sec., Center for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3823.

February 19-20—**Computerized Scanning of Body and Head—10th Annual Leo G. Rigler Radiology Seminar.** UCLA at Beverly Hilton Hotel, Beverly Hills. Saturday-Sunday.

March 5-6—**Diagnostic Nuclear Imaging.** UCSF at Fairmont Hotel, San Francisco. Saturday-Sunday.

March 7-11—**Diagnostic Radiology 1977.** UCSF at Fairmont Hotel, San Francisco. Monday-Friday.

March 12-13—**A Practical Course in Ultrasound.** UCSF at Fairmont Hotel, San Francisco. Saturday-Sunday.

March 17-19—**Annual Western-International CT Scanning Symposium.** Memorial Hospital Medical Center, Long Beach. Thursday-Saturday. 15 hrs. $200. Contact: Margaret Frederick, Center for Health Education, Memorial Hosp. Med. Ctr., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3823.

March 27-31—**Radiological Approach to Pediatric Problems.** USC at Bonaventure Hotel, Los Angeles. Sunday-Thursday.

April 29-30—**Sierra Valley Nuclear Medicine Association—Annual Symposium.** Sahara Tahoe Hotel, South Lake Tahoe. Friday-Saturday. Contact: Martha Frazer, Mercy San Juan Hospital, Dept. of Nuclear Medicine, 6501 Coyle Ave., Carmichael 95608.

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SURGERY AND ANESTHESIOLOGY

January 7-9—**Pathogenesis and Treatment of Headache and Other Head Pain in Adults and Children.** See Medicine, January 7-9.

January 13-14—**Phaco-Fragmentation.** UCSF. Thursday-Friday.

January 17-21—**Otologic Surgery Course—12th Annual.** Ear Research Institute, Los Angeles. Saturday-Wednesday. 45 hrs. $500. Contact: F. H. Linthicum, Jr., MD, Ear Research Institute, 256 S. Lake St., Los Angeles 90057.

January 22-23—**Dermatologic Surgery.** UCSF. Saturday-Sunday.

January 22-23—**Pediatric Urologic Seminar.** See Pediatrics, January 22-23.

January 23-27—**Midwinter Clinical Convention.** Research Study Club of Los Angeles at Hilton Hotel, Los Angeles. Sunday-Thursday. Contact: Research Study Club of Los Angeles, Inc., Box 49412, Los Angeles 90049. (213) 879-0143.

January 26-28—**Advances in Neurology.** See Medicine, January 26-28.

January 28-30—**Pediatric Anesthesiology—15th Clinical Conference.** Children's Hospital of Los Angeles at Marriott Hotel, Los Angeles. Friday-Sunday. 15 hrs. $125. Contact: Wayne Herbert, MD, Prog. Dir., CHLA, 4650 Sunset Blvd., Los Angeles 90054. (213) 660-2450, ext. 2262.

January 30-February 2—**Theodor Billroth Surgical Anatomy Course.** LLU. Sunday-Wednesday.

January 31-February 4—**Winter Symposium on Emergency Orthopedics.** American College of Emergency Physicians, Calif. Chapter, at Sahara Tahoe Hotel, Lake Tahoe. Monday-Friday. Contact: Stephanie McWilliams, Symposium Coordinator, ACEP, Calif. Chap., 58 California Ave., Orinda 94563. (415) 254-1332.

February 3-4—**Phaco-Fragmentation.** UCSF. Thursday-Friday.

February 4—**A Simplified Approach to Understanding Acid Base Balance—8th Travenlo Dinner Lecture.** Calif. Society of Anesthesiologists at Stanford Court, San Francisco. Friday. Contact: CSA, 100 S. Ellsworth Ave., Suite 806, San Mateo 94401. (415) 348-1407.

February 11—**Skin Antisepsis: Chlorhexidine Gluconate.** UCSF. Friday.

February 11-12—**Urodynamic Workshop I: Incontinence and Impotence.** UCLA. Friday-Saturday.

February 12-18—**Mid-Winter Nasal Symposium.** STAN at Harrah's, South Lake Tahoe. One week. $275; $175, residents. Contact: Willard E. Fee, Jr., MD, Division of Otolaryngology, Room 135, Stanford Univ. Medical Ctr., Stanford 94305. (415) 497-5828.

February 22-March 1—**Ventilatory and Circulatory Care of the Seriously Ill Patient.** Calif. Society of Anesthesiologists at Oahu and Kauai, Hawaii. One week. $125. Contact: Norm Catron, CSA, 100 S. Ellsworth St., San Mateo 94401. (415) 348-1407.

February 23-25—**Anterior Segment Disease in Surgery.** USC. 21 hrs. Wednesday-Friday.

February 23-27—**Controversial Areas in Surgery of the Head and Neck.** UCSD at Vacation Village Hotel, San Diego. Wednesday-Sunday. Contact: Alan M. Nahum, MD, 225 W. Dickinson St., San Diego 92103. (714) 294-5910.

March 2-4—**Acute Respiratory Failure in Black and White.** See Medicine, March 2-4.

March 3-4—**Oculoplastic Surgery.** UCSF. Thursday-Friday.

March 3-7—**Controversial Areas in Surgery—14th Annual Seminar.** UCLA at Palm Springs. Thursday-Monday.

March 7-11—**Surgical Forum.** Society of Graduate Surgeons of the Los Angeles County Hospital at Ambassador Hotel, Los Angeles. Monday-Friday. Contact: Miss Dee Davis, Exec. Sec. L.A. Obstetrical and Gynecological Society, 5410 Wilshire Blvd., Los Angeles 90036. (213) 937-5514.

March 8-12—**Vascular Surgery—5th Annual Symposium.** UCLA at Palm Springs. Tuesday-Saturday.

March 10-11—**Phaco-Fragmentation.** UCSF. Thursday-Friday.

March 11-12—**Ophthalmology Update I.** PMC at Golden Gateway Holiday Inn, San Francisco. Friday-Saturday.

March 11-12—**Retinal Disease.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Friday-Saturday. 12 hrs. $125. Contact: Margaret Frederick, Exec. Sec., Center for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3823.

March 11-12—**Symposium on Clinical and Technical Application of the Intra-Aortic Balloon Pump.** Daniel Freeman Hospital at Airport Park Hotel, Inglewood. Friday-Saturday. $100. Contact: Josephine Maxwell, Dept. of Education, Daniel Freeman Hospital, 333 N. Prairie Ave., Inglewood 90301. (213) 674-7050, ext 112.

March 13-17—**American Urological Association, Western Section.** Fairmont Hotel, San Francisco. Sunday-Thursday. 25 hrs. $170 for members; $195, nonmembers. Contact: Frank J. DeSantis, Exec. Sec., 21510 S. Main St., Carson 92037. (213) 549-3470.

March 14-18—**Anesthesiology 1977.** Anesthesiology Educational Foundation at Mammoth Lakes. Monday-Friday. Contact: Ronald L. Katz, MD, Dept. of Anesthesiology, UCLA School of Medicine, Los Angeles 90024.

March 17-19—**Plastic Ophthalmic Surgery: Intraocular Lenses Insertion.** St. Mary's Hospital and Medical Center, San Francisco. Thursday-Saturday. 24 hrs. $250. Contact: J. A. Sarrail, MD, 450 Sutter St, San Francisco. (415) 397-1500.

March 25-27—**Gynecological Urology.** See Obstetrics and Gynecology, March 25-27.

March 28-31—**American College of Surgeons—5th Annual Spring Meeting.** Bonaventure Hotel, Los Angeles. Monday-Thursday. Contact: Edwin W. Gerrish, MD, Asst. Dir., Assembly, ACS, 55 E. Erie St., Chicago 60611. (312) 664-4050.

March 31-April 1—**Diseases of the Urinary Tract.** STAN at Rickey's Hyatt House, Palo Alto. Thursday-Friday. 16 hrs. $150.

April 4-6—**American Association of Pediatric Ophthalmology.** See Pediatrics, April 4-6.

April 7-9—**Orbital Surgery.** UCLA. Thursday-Saturday.

April 14-15—**Office Orthopedics.** See Of Interest To All, April 14-15.

April 15-16—**Tendon and Nerve Injuries of the Hand.** PMC. Friday-Saturday.

April 21-22—**Diagnosis and Clinical Management of Glaucoma.** Jules Stein Eye Institute at Century Plaza Hotel, Los Angeles. Thursday-Friday. Contact: Jules Stein Eye Institute, UCLA School of Medicine, Los Angeles 90024.

April 21-22—**Phaco-Fragmentation.** UCSF. Thursday-Friday.

April 21-23—**General Surgery—Annual Course.** Thursday-Saturday.

April 23—**Audiology for Practicing Physicians.** PMC. Saturday.

April 28-29—**Current Problems in Intensive Care: Mechanical Ventilation.** UCSF at Stanford Court Hotel, San Francisco. Thursday-Friday. $125.

April 30—**Flexible Bronchofibroscopy.** PMC. Saturday.

April 30-May 7—**Management of the Surgical Patient.** STAN at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week $275.

Orthopaedic Audio-Synopsis Foundation. A non-profit service for Orthopaedic Surgeons publishing monthly recorded teaching programs which include summaries of pertinent literature and excerpts from national and international orthopaedic meetings. Monthly c-60 cassette tapes. Annual subscription rate $75 ($37.50 for residents). Contact: A. Harris, Man. Ed., OASF, 1510 Oxley St., So. Pasadena 91030. (213) 682-1760.

OF INTEREST TO ALL PHYSICIANS

January 18-21—**Diagnosis and Management of Seizure Disorders.** UCLA at Palm Springs. Tuesday-Friday.

January 22—**Gerontology.** John Muir Hospital and Walnut Creek Based Educational Committee at John Muir Hospital, Walnut Creek. Saturday. Contact: Marshall Y. Kremers, MD, 2528 Ptarmigan Dr., No. 3, Walnut Creek 94595. (415) 938-0568.

January 22-23—**Biofeedback and Meditation: Stress and Self-Regulatory Therapies.** UCSF and The Institute for the Study of Human Knowledge. Saturday-Sunday. 12 hrs. Contact: Ms. Mae Ling Yee, Cont. Ed. in Health Sciences, Room 135G, UCSF. (415) 666-2894.

January 22-February 27—**Basic Acupuncture.** PMC. Saturdays and Sundays. $1,100.

January 24-28—**Emergency Medicine.** UCLA at Beverly-Hilton Hotel, Beverly Hills, Monday-Friday.

January 24-28—**Topics in Emergency Medicine.** UCSF at Franklin Hospital, San Francisco. Monday-Friday.

January 25-28—**New Concepts of Old Diseases.** American College of Physicians at Letterman Army Medical Center, San Francisco. Tuesday-Friday. Contact: Registrar, Postgraduate Courses, ACP, 4200 Pine St., Philadelphia, PA 19104.

January 29—**Hypertension.** USC. Saturday.

January 31-February 4—**Winter Symposium on Emergency Orthopedics.** See Surgery, January 31-February 4.

January 31-February 5—**Family Practice Refresher Course.** UCI at Newporter Inn, Newport Beach. Monday-Saturday.

February 1-5—**Physician and Hospital.** USC at Ahwahnee Hotel, Yosemite. Tuesday-Saturday.

February 5-6—**Clinical Hypnosis and Behavior Modification.** See Psychiatry, February 5-6.

February 6-11—**Postgraduate Institute for Emergency Physicians, Symposium I.** UCSD at Hilton Hotel, San Diego. Sunday-Friday.

February 9-11—**Course for Physicians in Family Practice—27th Annual.** Mt. Zion Hospital and Medical Center, San Francisco. Wednesday-Friday. Contact: Office of Continuing Medical Education, Mt. Zion Hospital and Medical Center, P.O. Box 7921, San Francisco 94120. (415) 567-6600.

February 9-11—**Conference on Winter Sports Medicine—2nd Annual.** CMA, Medical Foundation of Santa Barbara County and UCLA at Mammoth Mountain. Wednesday-Friday. Contact: CMA.

February 9-12—**Primary Care—Current Management of Common Office Problems.** UCSF. Wednesday-Saturday.

February 11—**Skin Antisepsis: Chlorhexidine Gluconate.** See Surgery, February 11.

February 11-13—**American Medical Association—Regional Meeting.** Sahara Tahoe Hotel, Lake Tahoe. Friday-Sunday. Contact: Mr. G. K. Jewett, Dir., Dept. of Cont. Ed. Seminars, AMA, 535 N. Dearborn St., Chicago 60610. (312) 751-6000.

February 14-18—**Interpretive Enzymology.** UCSD at Airport Sheraton, San Diego. Tuesday-Saturday.

February 16—**Diagnostic Horizons 1977—15th Annual Symposium.** Eden Hospital at Willow Park Restaurant, Castro Valley. Wednesday. $35. Contact: E. Gregory Thomas, MD, Eden Hospital, 20103 Lake Chabot Rd., Castro Valley 94546. (415) 537-1234, ext. 213.

February 20-25—**Advances in Patient Care—4th Annual Conference.** Medical Communications and Services Assn. at Maui Surf Hotel, Maui, Hawaii. Sunday-Friday. 24 hrs. $175. Contact: Spring Zoog, Conf. Coordinator, MCSA, 315 U-District Bldg., 1107 N.E. 45th St., Seattle 98105. (206) 633-0505.

February 22-26—**Sports Medicine—Ski Injuries.** UCSF at Lake Tahoe. Tuesday-Saturday.

February 26—**Workshop for Physicians and Health Professionals.** UCLA. Saturday.

February 26—**Understanding the Histanic Patient.** PMC at University of San Francisco. Saturday.

February 28-March 4—**Basic Science for Clinicians.** STAN. Monday-Friday. $250.

March 4—**Diabetes Program—4th Annual.** UCD at Red Lion Motor Inn, Sacramento. Friday.

March 4-9—**California Medical Association—106th Annual Session.** Disneyland Hotel, Anaheim. Friday-Wednesday. Contact: Gail Jara, CMA.

March 8-12—**Sports Medicine for the Primary Physician.** Univ. of Hawaii School of Medicine and American Academy of Family Physicians at Princess Kaiulani Hotel, Honolulu. Tuesday-Saturday. 18 hrs. $200. Contact: Mr. Harold Brown, Hawaii Conferences Services, P.O. Box 22670, Honolulu 96822.

March 13-17—**Association for the Advancement of Medical Instrumentation—12th Annual Meeting.** Hyatt Regency Hotel, San Francisco. Sunday-Thursday. Contact: Michael J. Miller, Exec. Dir., AAMI, 1901 N. Ft. Myer Dr., Suite 602, Arlington, Va. 22209. (703) 525-4890.

March 16-April 16—**Family Medicine Tutorial.** DREW. Wednesday mornings.

March 18-24—**LLU School of Medicine—Annual Postgraduate Convention.** Friday-Thursday. Contact: Alumni Association, LLU.

March 26—**Prevention of Athletic Injuries.** Sonoma County Medical Assn. at Calif. State College, Sonoma, Rohnert Park. Saturday. Contact: William E. Tewksbury, Asst. Exec. Dir., SCMA, 3452 Mendocino Ave., Santa Rosa 95401. (707) 544-2010.

March 26-27—**Practical Endocrinology for the Primary Care Physician.** UCLA. Saturday-Sunday. 12 hrs. $125.

March 28-29—**Current Problems in Intensive Care.** UCSF. Monday-Tuesday.

March 28-April 1—**Postgraduate Institute for Emergency Physicians, Symposium II.** UCSD. Monday-Friday.

March 28-April 1—**Therapy: Principles and Use of Drugs.** STAN. Monday-Friday.

April 1-2—**West Coast Counties Postgraduate Institute.** CMA at Quail Lodge, Carmel. Friday-Saturday.

April 2—**Total Parenteral Nutrition.** PMC. Saturday.

April 13-14—**American Geriatrics Society—34th Annual Meeting.** San Francisco. Wednesday-Thursday. Contact: Marcia Roye, Assoc. Exec. Dir., AGS, 10 Columbus Cir., New York 10019. (212) 582-1333.

April 14-15—**Newer Trends and Practical Issues in the General Care of the Aged.** UCSF. Thursday-Friday.

April 14-15—**Office Orthopedics.** USC. Thursday-Friday.

April 15-16—**Aches, Pain and Dramatic Diseases in Children and Young Adults.** See Pediatrics, April 15-16.

April 16-23—**Emergency Medicine.** USC at Kona Surf Hotel, Kona, Hawaii. One week.

April 18-22—**Intensive Review of Family Practice.** USC. Monday-Friday.

April 22-24—**Family Medicine Intensive Review.** DREW. Friday-Sunday.

April 23—**Audiology for Practicing Physicians.** See Surgery, April 23.

April 29-30—**San Joaquin Valley Counties Postgraduate Institute.** CMA at Ahwahnee Hotel, Yosemite. Friday-Saturday.

April 30-May 1—**Psychological and Medical Management of Stress.** See Psychiatry, April 30-May 1.

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PRECEPTORSHIPS AND TRAINEESHIPS

Training for Physicians in General Internal Medicine. LLU. Four weeks or more, by arrangement. Bedside and classroom training, practical aspects of clinical care and management. 160 hrs. Contact: John E. Peterson, MD, LLU.

Training of Physicians in Modern Concepts of Pulmonary Care. LLU. Four weeks or more, by arrangement. Diagnostic and therapeutic methods in medical chest disease, physiological methodology of modern pulmonary care programs, use of new instrumentation in the field. 160 hrs. Contact: John E. Hodgkin, MD, Chief, Section of Medical Chest Diseases, LLU.

Physician-in-Residence Preceptorship in Pulmonary Disease. USC, Pulmonary Disease Section, Dept. of Medicine and Postgraduate Medical Education. One month or more, by arrangement. Opportunity for practicing physician to achieve specified knowledge and skills in adult pulmonary medicine. Contact: Oscar J. Balchum, MD, PhD, USC.

Training for Physicians in Nephrology. LLU. Four weeks or more, by arrangement. Hemodialysis, peritoneal dialysis, renal biopsy, and kidney transplantation. 160 hrs. Contact: Robert E. Soderblom, MD, LLU.

Preceptorships in Cardiology. PMC. By arrangement. $200 per mo.; $500 for 3 mos. Contact: Arthur Selzer, MD, PMC.

Preceptorships in Practical Office Dermatology. PMC. Wednesdays or Fridays, 9:00 a.m.-12:00 noon, for 10 weeks. Periods begin Oct., Jan., or April. $100. Contact: Harold M. Schneidman, MD, Dept. of Dermatology, PMC.

Preceptorships in Infectious Disease. PMC. Full time for four weeks. To be arranged. $250. Contact: Rodney J. Valentine, MD, Chief, Div. of Infectious Diseases, PMC.

Preceptorships in Basic Sciences, Biochemistry and Biophysics, Dermatology, Echocardiography, International Health, Microbiology, Neurological Surgery, Obstetrics and Gynecology, Pediatrics, Pharmacology and Experimental Therapeutics, Physiology, Psychiatry, Urology. UCSF. By special arrangement.

Traineeships in Renal Dialysis. UCSF. By special arrangement.

OREGON

COUNCIL ON MEDICAL EDUCATION

THIS BULLETIN of information regarding continuing education programs and meetings of various medical organizations in Oregon is supplied by the Council on Medical Education of the Oregon Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Council on Medical Education, Oregon Medical Association, 5210 S.W. Corbett Ave., Portland, OR 97201; or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

University of Oregon Medical School, Department of Internal Medicine, 3181 S.W. Sam Jackson Park Road, Portland 97201:

Every Tuesday, 8:00 a.m. to 9:00 a.m.—**Internal Medicine Grand Rounds.** Library Auditorium, University of Oregon Health Sciences Center, Portland. Contact: Stephen R. Jones, MD, Department of Internal Medicine, University of Oregon Health Sciences Center, 3181 S.W. Sam Jackson Park Road, Portland, 97201.

FAMILY PRACTICE

Every Wednesday, 11:00 a.m. to 12:00 Noon. **Family Practice Grand Rounds.** Family Practice Center, University of Oregon Health Sciences Center. Contact: William A. Fisher, MD, University of Oregon Health Sciences Center, Dpartment of Family Practice, 3181 S.W. Sam Jackson Park Road, Portland 97201.

February 14-18—**Family Practice Review.** Sheraton Hotel, Lloyd Center, Portland. Contact: William A. Fisher, MD, Department of Family Practice, University of Oregon Health Sciences Center, 3181 S.W. Sam Jackson Park Road, Portland 97201.

INTERNAL MEDICINE

Every Tuesday, 8:00 a.m. to 9:00 a.m.—**Internal Medicine Grand Rounds.** Library Auditorium, University of Oregon Health Sciences Center, Portland. Contact: Stephen Jones, MD, Department of Internal Medicine, University of Oregon Health Sciences Center, 3181 S.W. Sam Jackson Park Road, Portland 97201.

SURGERY

January 28—**Portland Surgical Society.** Benson Hotel, Portland. Contact: William C. Awe, MD, 2222 N.W. Lovejoy #202, Portland 92710.

OF INTEREST TO ALL PHYSICIANS

January 21—**Lung Cancer—Current Management: 1977.** Portland Hilton Hotel, Portland. Contact: William P. Galen, MD, 2311 N.W. Northrup, Portland 97210.

February 4—**Annual Lederle Symposium.** Sheraton Hotel, Lloyd Center, Portland. Contact: Peter DeWitt, MD, 6274 S.W. Capitol Highway, Portland 97201.

February 10-11—**Current Concepts in Exercise Testing and Training in Coronary Heart Disease.** YMCA, Portland. Contact: J. S. Reinschmidt, MD, Division of Continuing Medical Education, University of Oregon Health Sciences Center, 3181 S.W. Sam Jackson Park Road, Portland 97201.

February 17-19—**Oregon Thoracic Society Annual Chest Disease Conference.** Salishan Lodge, Gleneden Beach, Oregon. Contact: Max R. Mehlhaff, Executive Secretary, Oregon Thoracic Society, 1020 S.W. Taylor St., Portland 97205.

March 11—**Urology Day.** Sacred Heart General Hospital, Eugene. Contact: Kenneth Blundon, MD, 132 E. Broadway, Eugene 97401.

April 13-15—**University of Oregon Health Sciences Center Annual Alumni Meeting and Sommer Memorial Lectures.** Library Auditorium, University of Oregon Health Sciences Center. Contact: Michele Wiley, Medical Relations Officer, University of Oregon Health Sciences Center, 3181 S.W. Sam Jackson Park Road, Portland 97201.

WASHINGTON, ALASKA, MONTANA AND IDAHO

In order to have future activities listed here or to receive information on these and other activities, please write Ms. Joan M. Kelday, Information Specialist, Continuing Medical Education, WAMI Program, University of Washington School of Medicine, Health Sciences Building, SC-64, Seattle, Washington 98195. Phone: (206) 543-6995.

January 19—**Perinatal Health Care.** Wednesday. Univ. of Wash. in Anacortes, Wash. 7:30-10 a.m., Island Hospital. 2½ hrs. Contact: Harry Eiesland, MD, 24th and M Ave., Anacortes, WA 98221. (206) 293-3101.

January 24—**Internal Medicine Review: Hematology.** Monday. Univ. of Wash. in Wenatchee, Wash. 7:30-9:30 p.m., Wenatchee Valley Clinic. 2 hrs. Contact: William M. McKee, MD, P.O. Box 489, Wenatchee, WA 98801. (509) 663-8711.

January 25—**Internal Medical Review: Hematology.** Tuesday. Univ. of Wash. in Yakima, Wash. 5-7 p.m., Memorial Hospital. 2 hrs. Contact: Harry R. Kimball, MD, Yakima Medical Center, Suite 5, Yakima, WA 98902. (509) 248-6791.

January 27—**Internal Medicine Review: Immunologic Renal Disease.** Thursday. Univ. of Wash. in Billings, Mont. 7-9:30 a.m., Marillac Hall. 2½ hrs. Contact: Mrs. Frances Burt, Cont. Med. Ed., Marillac Hall, Billings, MT 59101. (406) 252-2121, Ext 258.

January 27—**Radiation-Oncology.** Thursday. 7:30-10:30 p.m., Tacoma General Hospital, Tacoma, Wash. 3 hrs. Contact: Mrs. Maxine Bailey, College of Medical Education, The University of Puget Sound, 1500 N. Warner, Tacoma, WA 98416. (206) 756-3152.

January 28—**Internal Medicine Review: Immunologic Renal Disease.** Friday. Univ. of Wash. in Missoula, Mont. 8:30-11 a.m., St. Patrick Hospital. 2½ hrs. Contact: James E. Gouaux, MD, 515 Kensington, Missoula, MT 59801. (406) 549-4581.

January 28—**What's New in Liver-Biliary Disease.** Friday. Virginia Mason Medical Center Auditorium, Seattle. 6½ hrs. $50. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) 223-6898.

January 28-29—**Tax, Estate, and Financial Planning.** Friday-Saturday. Olympic Hotel, Seattle. Hours and fee to be determined. Contact: Pat Lind, Div. of CME, HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050 or 543-9495.

February 1—**Surgery: Chest Trauma and Diseases of the Lower Esophagus.** Tuesday. Univ. of Wash. in Missoula, Mont. 7-9 p.m., Community Hospital. 2 hrs. Contact: Leonard W. Brewer, MD, 2833 Ft. Missoula Rd., Missoula, MT 59801. (406) 728-6815.

February 2—**Surgery: Chest Trauma and Diseases of the Lower Esophagus.** Wednesday. Univ. of Wash. in Billings, Mont. 1-3:30 p.m., Marillac Hall. 2½ hrs. Contact: Mrs. Frances Burt, Cont. Med. Ed., Marillac Hall, Billings, MT 59101. (460) 252-2121, Ext 258.

February 4-5—**Modern Concepts of Epilepsy.** Friday-Saturday. Seattle. Location, hours, fee to be determined. Contact: Pat Lind, Div. of CME, HSB SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050 or 543-9495.

February 9-10—**University of Washington School of Medicine Circuit Course on Pain.** Feb. 9, Longview, Wash.; Feb. 10, Olympia, Wash. 4 hrs. Physicians, $25; others, $15. Contact: Pat Lind, Div. of CME, HSB SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050 or 543-9495.

February 10-11—**Medical and Surgical Aspects of Urinary Tract Disease.** Thursday-Friday. Virginia Mason Medical Center Auditorium, Seattle. 13 hrs. $75. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) 223-6898.

February 11-12—**Coronary Care Ski Weekend.** Friday-Saturday. Big Sky, Mont. Hrs. and fee to be determined. Contact: John Breedon, Exec. Dir., Montana Medical Education Research Foundation, P.O. Box 2829, Great Falls, MT 59403. (406) 453-1491.

February 12-19—**Critical Care: Maternal/Perinatal.** Saturday-Saturday. Univ. of Wash. in Sun Valley, Idaho. 38 hrs. Physicians, $150; others $100. Contact: Pat Lind, Div. of CME, HSB SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050 or 543-9495.

February 15-18—**Gastrointestinal Disease.** Tuesday-Friday. 8-10 a.m., St. Joseph Hospital, Tacoma, Wash. 8 hrs. Contact: Mrs. Maxine Bailey, College of Medical Education, The University of Puget Sound, 1500 N. Warner, Tacoma, WA 98416. (206) 756-3152.

February 24-25—**Modern Concepts in Allergy.** Thursday-Friday. Virginia Mason Medical Center Auditorium, Seattle. Hours to be determined. $75. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) 223-6898.

February 24-25—**Atherosclerosis.** Thursday-Friday. Seattle. Location, hours, fee to be determined. Contact: Pat Lind, Div. of CME, HSB SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-9495 or 543-1050.

February 24—**Internal Medicine Review: Liver and Pancreatic Diseases.** Univ. of Wash. in Billings, Mont. 7-9:30 a.m., Marillac Hall, 2½ hrs. Contact: Mrs. Frances Burt, Cont. Med. Ed. Marillac Hall, Billings, MT 59101. (406) 252-2121, Ext. 258.

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February 28-March 1—**Emergency Medicine.** Monday-Friday. Seattle. Location, hours, fee to be determined. Contact: Pat Lind, Div. of CME, HSB SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-9495 or 543-1050.

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March 11—**Cardiovascular Orientation.** Friday. Tacoma General Hospital, Tacoma, Wash. 3 hrs. Contact: Mrs. Maxine Bailey, College of Medical Education, The University of Puget Sound, 1500 N. Warner, Tacoma, WA 98416. (206) 756-3152.

March 12—**Depression and Insomnia.** Saturday. Seattle. Location, hours, fee to be determined. Contact: Pat Lind, Div. of CME, HSB SC-50, Univ. of Wash. School of Med., Seattle 98195. (206) 543-9495 or 543-1050.

March 16—**Metabolic Disorders in Pediatrics.** Wednesday. Univ. of Wash. in Ancortes, Wash. 7:30-10 a.m., Island Hospital, 2½ hrs. Contact: Harry Eiesland, MD, 24th and M Ave., Ancortes, WA 98221. (206) 292-3101.

March 17-18—**What's New in Internal Medicine.** Thursday-Friday. St. Joseph Hospital, Tacoma, Wash. 12 hrs. Contact: Mrs. Maxine Bailey, College of Medical Education, The University of Puget Sound, 1500 N. Warner, Tacoma, WA 98416. (206) 756-3152.

March 18-19—**Otolaryngologic and Head and Neck Emergencies.** Friday-Saturday. Virginia Mason Medical Center Auditorium, Seattle. Hours and fee to be determined. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) 223-6898.

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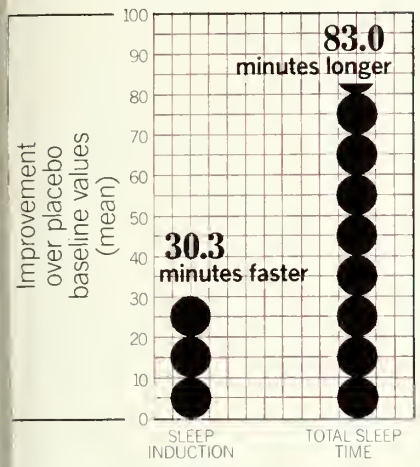

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REFERENCES:
1. Frost JD Jr: Data on file, Medical Department, Hoffmann-La Roche Inc., Nutley NJ
2. Data on file, Medical Department, Hoffmann-La Roche Inc., Nutley NJ
3. Robinson DS, Amidon EL: Interaction of benzodiazepines with warfarin in man, in *The Benzodiazepines*, edited by Garattini S, Mussini E, Randall LO. New York, Raven Press, 1973, p. 641

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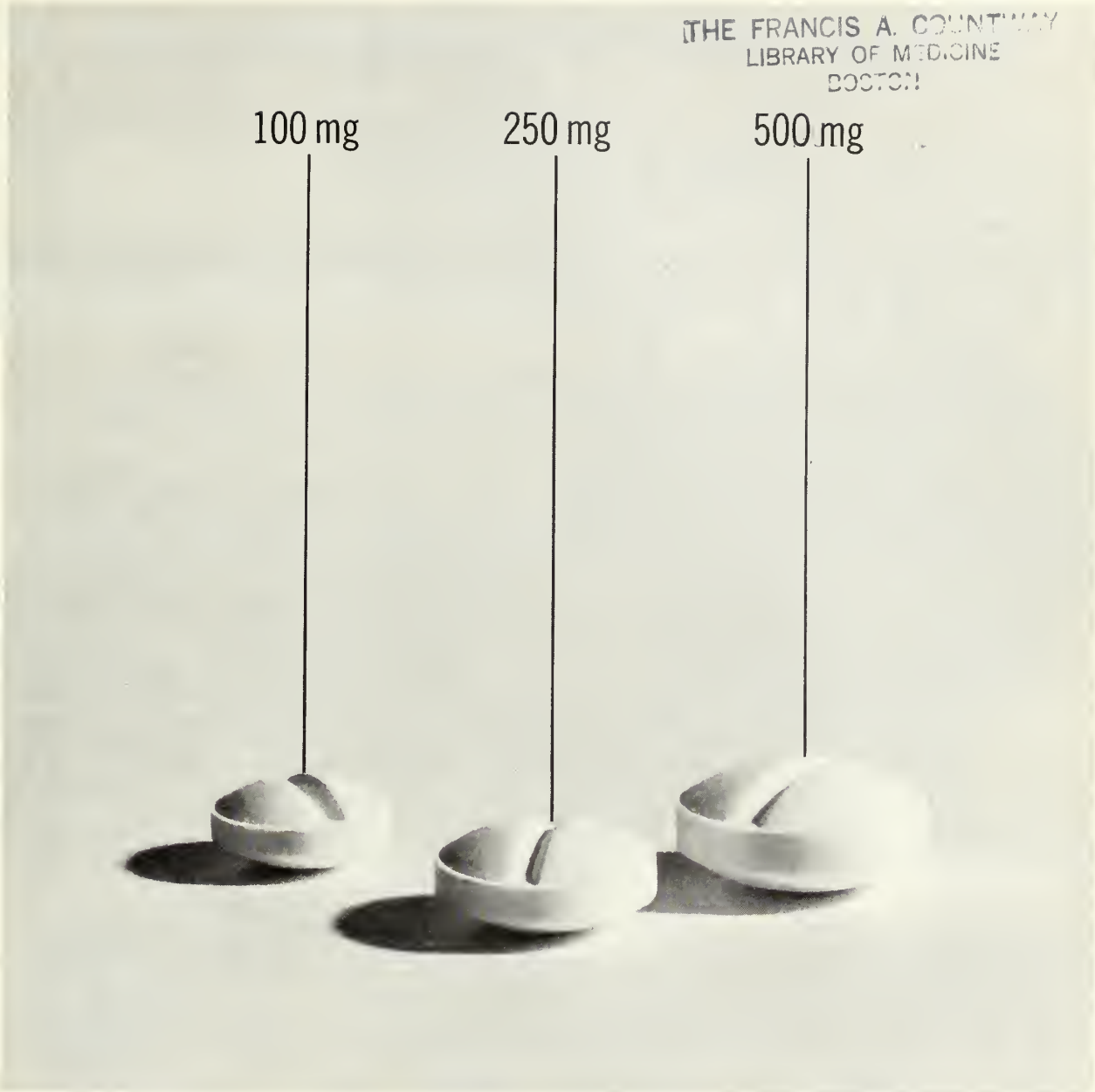

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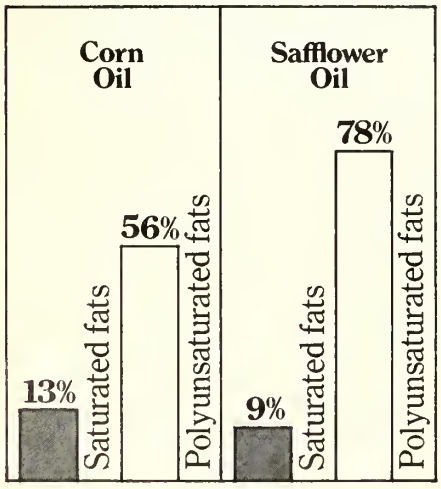

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efore prescribing, see complete prescribing information in SK&F Co. literature or PDR. A rief summary follows:

WARNING
This fixed combination drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual patient. If the fixed combination represents the dosage so determined, its use may be more convenient in patient management. The treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

ndications: When the fixed combination represents the dosage determined by titration: Adjunctive therapy in edema associated with congestive eart failure, hepatic cirrhosis, the nephrotic yndrome. Corticosteroid and estrogen-induced dema, idiopathic edema; hypertension, when he potassium-sparing action of its 'Dyrenium' omponent is warranted.

ontraindications: Further use in progressive enal or hepatic dysfunction; hyperkalemia. Preexisting elevated serum potassium. Hypersensivity to either component or other sulfonamideerived drugs. Routine use of diuretics in therwise healthy pregnancy.

Varnings: Do not use potassium supplements, ietary or otherwise, unless hypokalemia delops or dietary intake of potassium is markedly npaired. If supplementary potassium is needed, otassium tablets should not be used. Hyperalemia can occur, and has been associated with cardiac irregularities. **It is more likely in severely ill patients with urine volume less than one liter/day, the elderly or diabetics, with suspected or confirmed renal insufficiency.** Periodic determinations of serum K^+ should be made. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **The presence of a widened QRS complex or arrhythmia in association with hyperkalemia requires prompt additional therapy.** Thiazides are reported to cross the placental barrier and appear in breast milk; fetal or neonatal hyperbilirubinemia, thrombocytopenia, altered carbohydrate metabolism and other adverse reactions that have occurred in the adult may result. When used in pregnancy or in women who might bear children, weigh potential benefits against possible hazards to fetus. Adequate information on use in children is not available.

Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics, or those with suspected or confirmed renal insufficiency. Watch for signs of impending coma in severe liver disease. If spironolactone is used concomitantly, determine serum K^+ frequently; both can cause K^+ retention and elevated serum K^+. Two deaths have been reported with such concomitant therapy (in one, recommended dosage was exceeded, in the other serum electrolytes were not properly monitored). Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving Dyrenium® (triamterene, SK&F Co.), and leukopenia, thrombocytopenia, agranulocytosis, and aplastic anemia have been reported with thiazides. Do periodic blood studies in cirrhotics to check for nondrug-related variations in blood pictures, and in patients with folic acid depletion, since 'Dyrenium' may contribute to appearance of megaloblastosis. Antihypertensive effect may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances. Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and, rarely, allergic pneumonitis have occurred with thiazides alone.

Supplied: Bottles of 100 and 1000 capsules; Single Unit Packages of 100 (intended for institutional use only).

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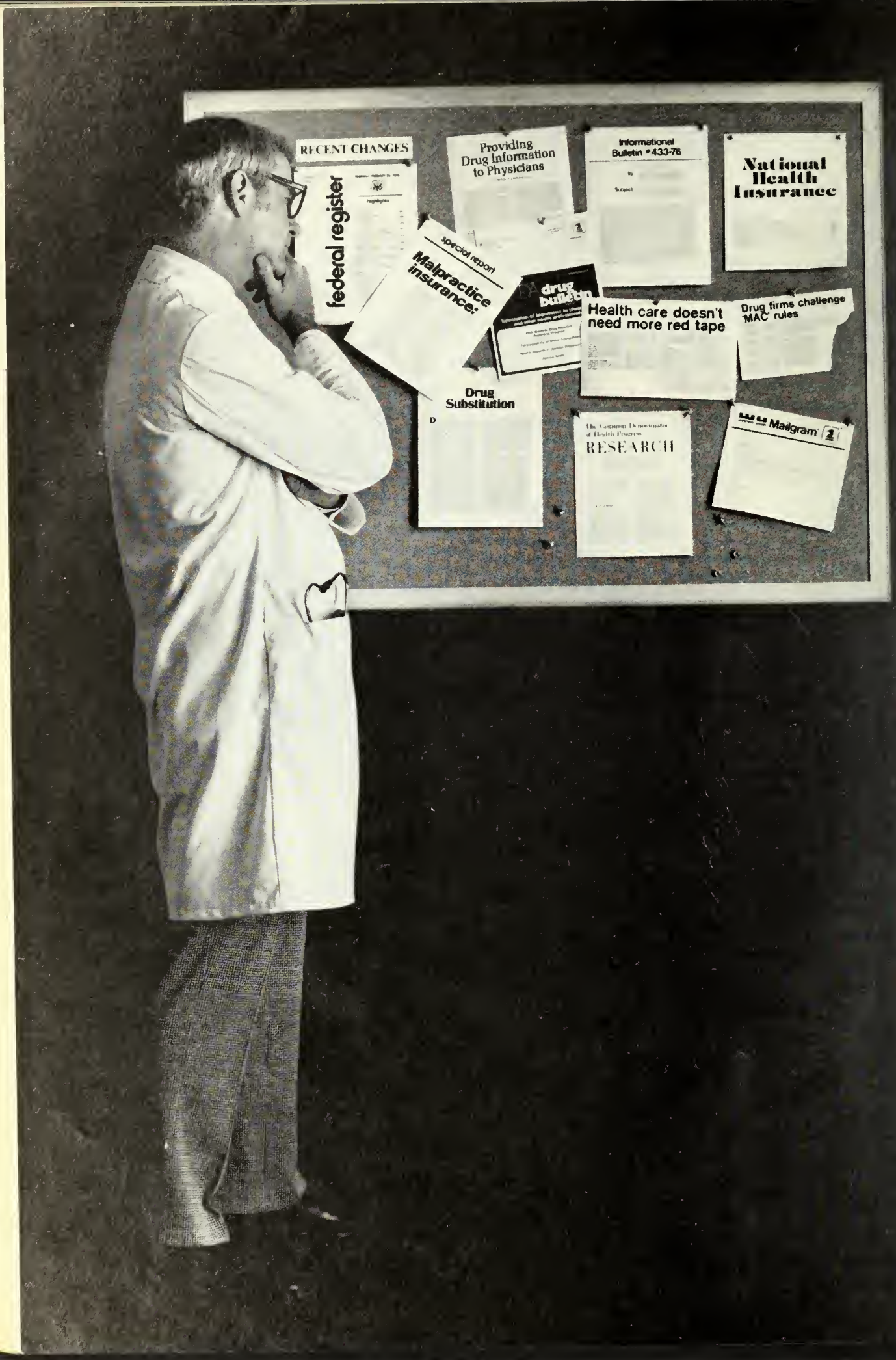
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THERE ARE A LOT OF PEOPLE GETTING BETWEEN YOU AND YOUR PATIENT.

Medicine today is in the spotlight, subjected to all kinds of scrutiny. Your control over patient therapy is being monitored, judged and occasionally abrogated, sometimes by unknown third parties.

The worry is that in the wake of this focus, the relationship between you and your patient will be weakened, without offsetting benefits. Consider three examples:

Drug substitution In most states, pharmacy laws, regulations or professional custom stipulate that your non-generic prescriptions be filled with the precise products you prescribe. But in the last five years, a dozen or more State laws have been changed, permitting the pharmacist in most cases to select a product of the same generic drug to fill any prescription.

Ironically, this dilution of physician control has taken place against a background of growing evidence that purportedly equivalent drug products may be inequivalent, since neither present drug standards nor their enforcement are optimal. In fact, the FDA itself says it has not enforced the same standards for hundreds of "follow-on" products that it had applied to the original NDA approvals. Thus physician control over patient therapy is being eroded with a risk that patients may be exposed to drugs of uncertain quality.

The major advertised claim for substitution is reduced prescription prices for consumers. Yet no documentation of any significant savings has been produced.

MAC Maximum Allowable Cost, MAC for short, is a Federal regulation designed to cut the Government's drug bill by setting price ceilings for drugs dispensed to Medicare and Medicaid patients. Unless the prescriber certifies on the prescription that a particular product is medically necessary, the Government intends to pay only for the cost of the lowest-priced, purportedly-equivalent, generally-available product. The effect of the program may be that elderly and indigent patients will be restricted to products which someone in Washington believes are priced right. Practicing doctors will have little to say about administration of the program, since Government will have absolute authority to make its choices stick.

The drug lag The future of drug and device research depends upon a scientific and regulatory environment that encourages therapeutic innovations. The American pharmaceutical industry annually is spending more than $1 billion of its own funds and evaluating more than 1,200 investigational compounds in clinical research. Disease targets include cancer, atherosclerosis, viruses and central nervous system disorders, among others. But there is a major barrier to the flow of new drugs to your patients: The cost of the research is more than ten times what it was, per product, in 1962; and whereas governmental clearance of new drug applications took six months then, it commonly consumes two years now.

The FDA needs adequate time, of course, to consider data. But it is equally clear that the present approval process contributes to needless delay of needed therapy. That's why the increased efficiency of the drug approval process is vital to all our futures.

If these issues concern you, we suggest that you make your voice heard—among your colleagues and your representatives in State legislatures and in Washington.

It could make a difference in your practice tomorrow.

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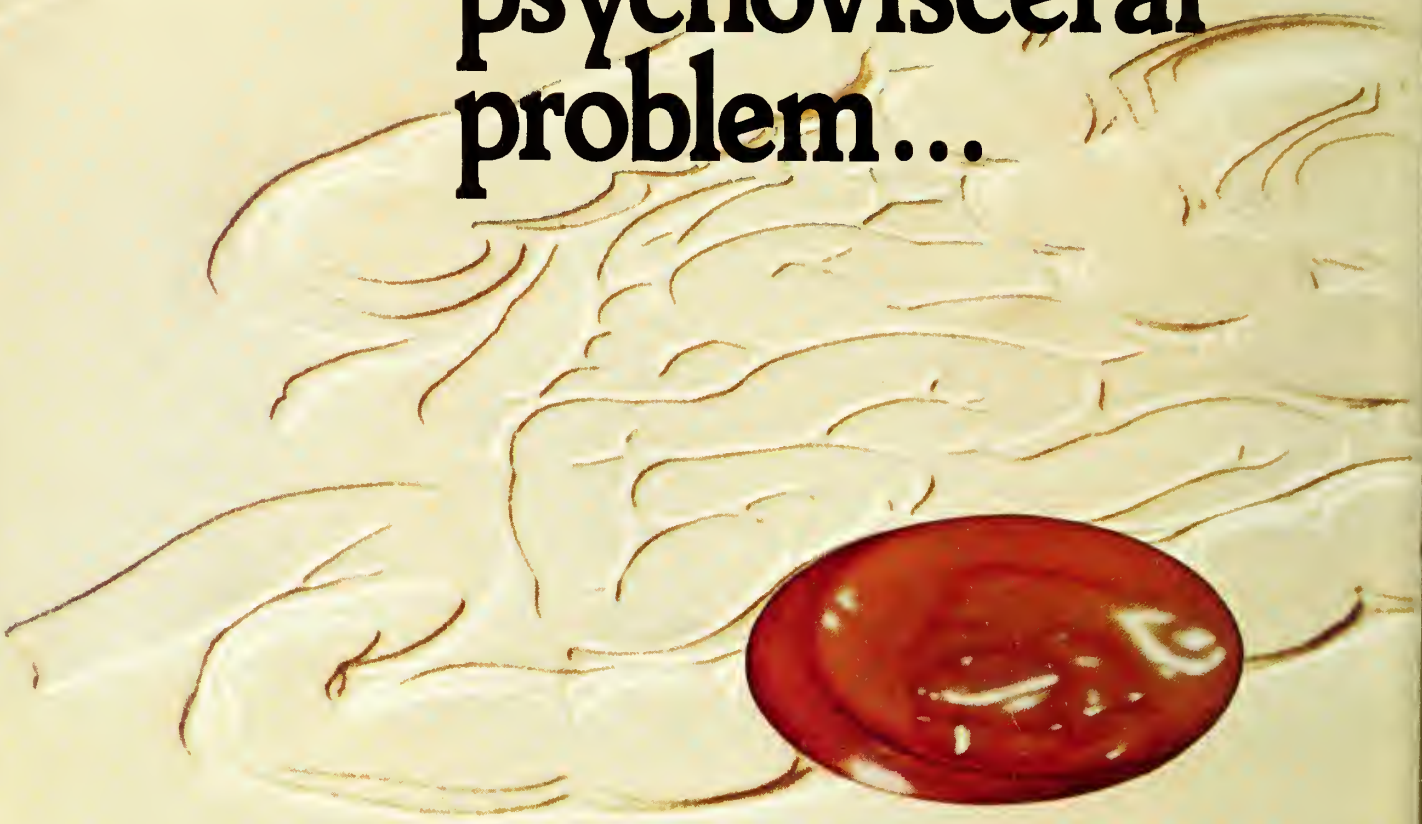
Because irritable bowel syndrome* is a psychovisceral problem...

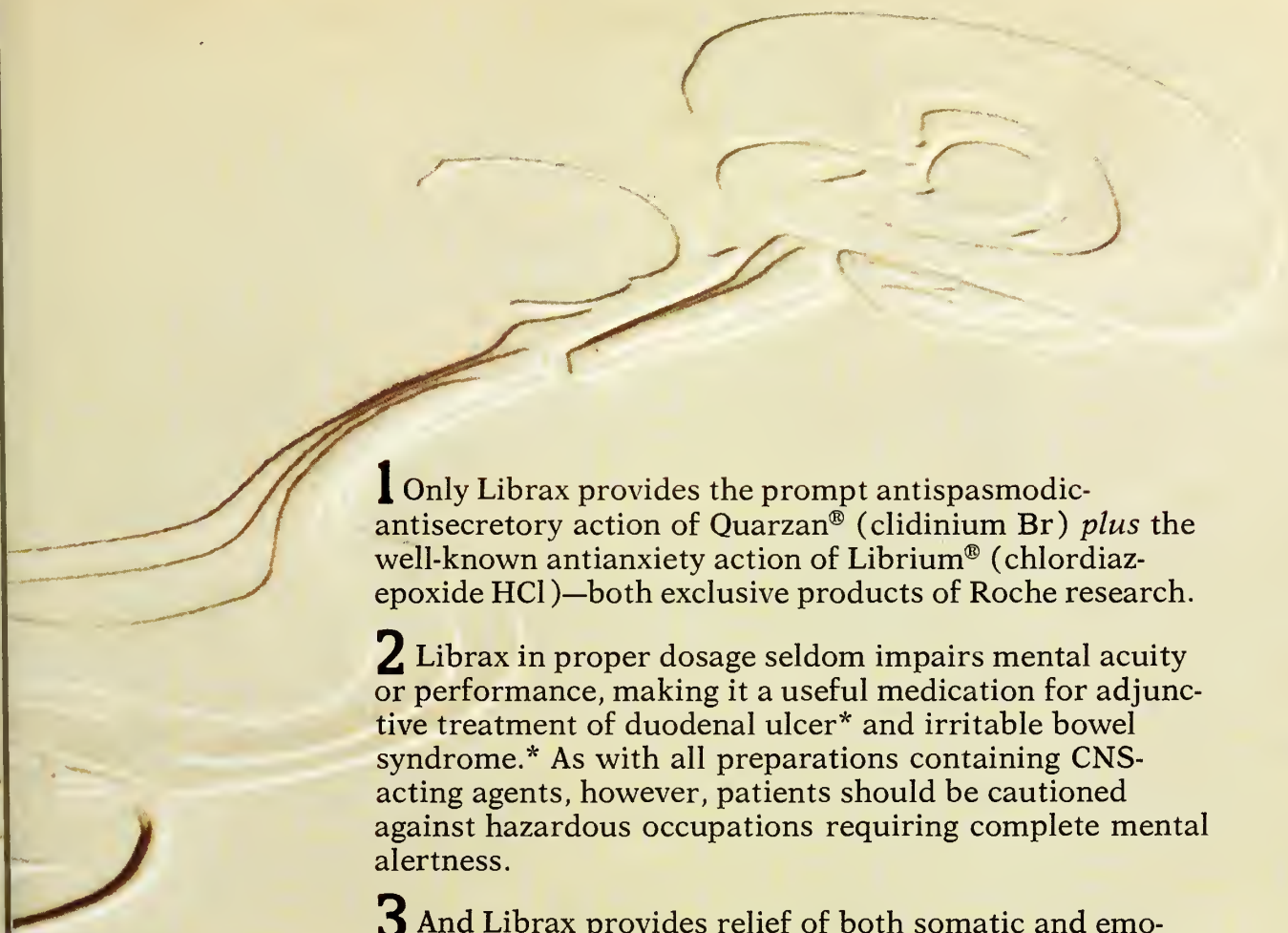


The symptoms of irritable bowel syndrome have long been recognized as functional concomitants of excessive anxiety and emotional tension. Relationships between emotionally charged life situations and disorders of colonic motility have even been demonstrated by means of stress-interview experiments.[1] And disturbed bowel function is often induced or aggravated by fluctuating psychologic states rather than organic disease.

After the patient history has been reviewed and organic disease excluded, the patient should be reassured as to the nature of his condition and treatment directed toward both the somatic and emotional aspects of the disorder. Adjunctive therapy with Librax is doubly valuable because it reduces not only painful symptoms due to colonic hypermotility but also underlying excessive anxiety and emotional tension.

[1]Almy TP: Irritable colon, chap. 100, in *Gastrointestinal Disease*, edited by Sleisenger MH, Fordtran JS. Philadelphia, W.B. Saunders Company, 1973, pp. 1281-1283.

***Librax has been evaluated as possibly effective for this indication. Please see brief summary of prescribing information on third page.**



1 Only Librax provides the prompt antispasmodic-antisecretory action of Quarzan® (clidinium Br) *plus* the well-known antianxiety action of Librium® (chlordiazepoxide HCl)—both exclusive products of Roche research.

2 Librax in proper dosage seldom impairs mental acuity or performance, making it a useful medication for adjunctive treatment of duodenal ulcer* and irritable bowel syndrome.* As with all preparations containing CNS-acting agents, however, patients should be cautioned against hazardous occupations requiring complete mental alertness.

3 And Librax provides relief of both somatic and emotional symptoms with the convenience and economy of a *single* capsule...all advantages in sustaining patient compliance.

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A distinctive antianxiety-anticholinergic agent

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se see following page for brief summary of prescribing information.

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A distinctive antianxiety-anticholinergic agent

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The initial prescription allows evaluation of patient response to therapy.

Follow-up

Follow-up therapy with a prescription for a 2- to 3-week supply of medication usually helps maintain patient gains.

Adjunctively for treatment of psychovisceral symptoms in irritable bowel syndrome* and duodenal ulcer*

Please consult complete prescribing information, a summary of which follows:

* **Indications:** Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:

"Possibly" effective: as adjunctive therapy in the treatment of peptic ulcer and in the treatment of the irritable bowel syndrome (irritable colon, spastic colon, mucous colitis) and acute enterocolitis.

Final classification of the less-than-effective indications requires further investigation.

Contraindications: Patients with glaucoma; prostatic hypertrophy and benign bladder neck obstruction; known hypersensitivity to chlordiazepoxide hydrochloride and/or clidinium bromide.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. As with all CNS-acting drugs, caution patients against hazardous occupations requiring complete mental alertness (e.g., operating machinery, driving). Though physical and psychological dependence have rarely been reported on recommended doses, use caution in administering Librium® (chlordiazepoxide hydrochloride) to known addiction-prone individuals or those who might increase dosage; withdrawal symptoms (including convulsions), following discontinuation of the drug and similar to those seen with barbiturates, have been reported.

Usage in Pregnancy: **Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

As with all anticholinergic drugs, an inhibiting effect on lactation may occur.

Precautions: In elderly and debilitated, limit dosage to smallest effective amount to preclude development of ataxia, oversedation or confusion (not more than two capsules per day initially; increase gradually as needed and tolerated). Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider pharmacologic effects of agents, particularly potentiating drugs such as MAO inhibitors and phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions (e.g., excitement, stimulation and acute rage) have been reported in psychiatric patients. Employ usual precautions in treatment of anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation have been reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship has not been established clinically.

Adverse Reactions: No side effects or manifestations not seen with either compound alone have been reported with Librax. When chlordiazepoxide hydrochloride is used alone, drowsiness, ataxia and confusion may occur, especially in the elderly and debilitated. These are avoidable in most instances by proper dosage adjustment, but are also occasionally observed at the lower dosage ranges. In a few instances syncope has been reported. Also encountered are isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent and generally controlled with dosage reduction; changes in EEG patterns (low-voltage fast activity) may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice and hepatic dysfunction have been reported occasionally with chlordiazepoxide hydrochloride, making periodic blood counts and liver function tests advisable during protracted therapy. Adverse effects reported with Librax are typical of anticholinergic agents, *i.e.*, dryness of the mouth, blurring of vision, urinary hesitancy and constipation. Constipation has occurred most often when Librax therapy is combined with other spasmolytics and/or low residue diets.

Dosage: Individualize for maximum beneficial effects. Usual maintenance dose is 1 or 2 capsules, 3 or 4 times a day, before meals and at bedtime. Geriatric patients—see Precautions.

How Supplied: Librax® Capsules, each containing 5 mg chlordiazepoxide hydrochloride (Librium®) and 2.5 mg clidinium bromide (Quarzan®)—bottles of 100 and 500; Prescription Paks of 50, available singly and in trays of 10.

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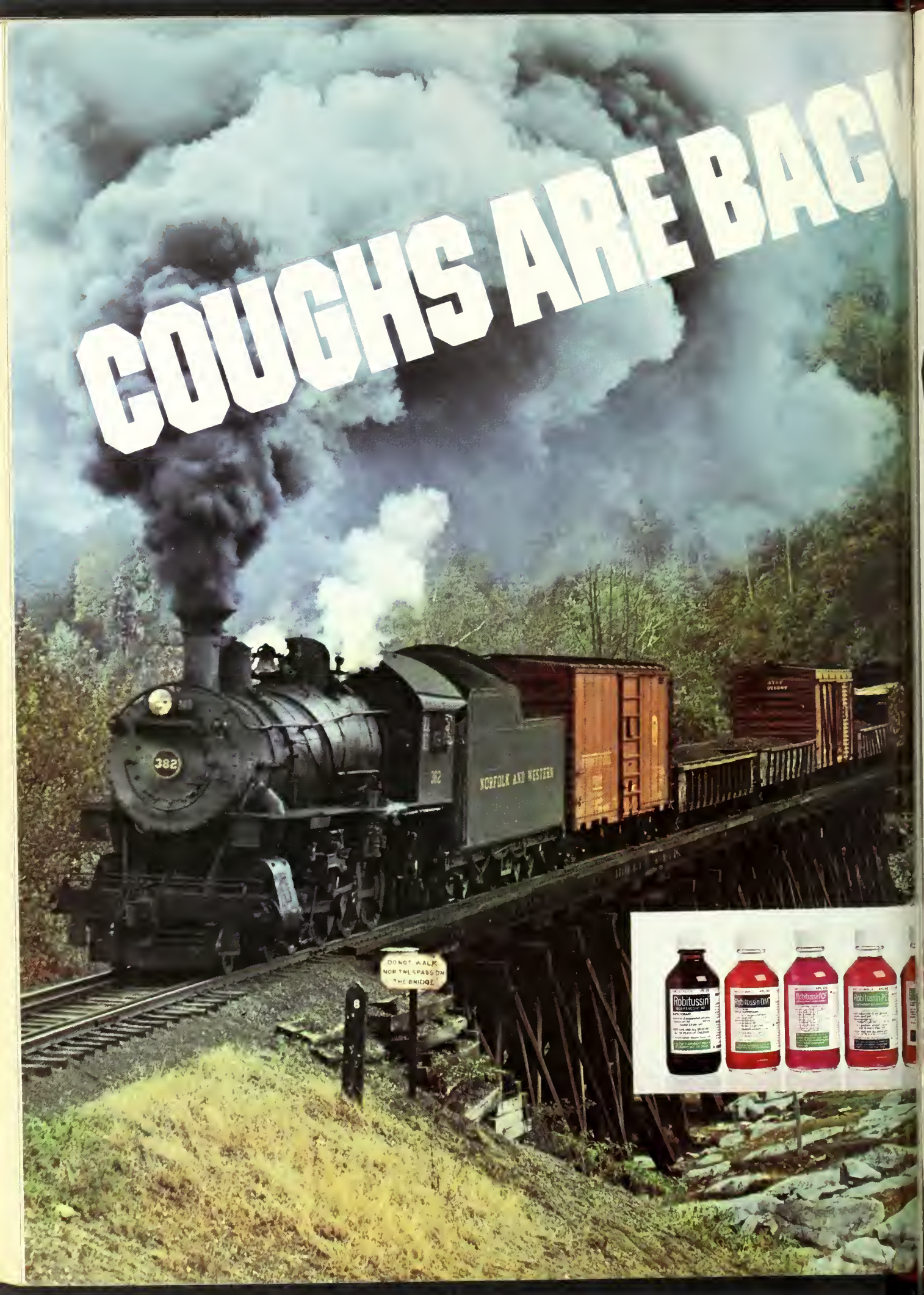
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Refer to: Freed C, Schiller NB: Echocardiographic findings in Marfan's syndrome. West J Med 126:87-90, Feb 1977

THE WESTERN
Journal of Medicine

Echocardiographic Findings in Marfan's Syndrome

CURT FREED, MD, *Denver, and* NELSON B. SCHILLER, MD, *San Francisco*

Echocardiographic studies of 11 patients with Marfan's syndrome showed that in all adult patients aortic root diameters were larger than 35 mm (normal range 24 to 35, mean 30±2 mm). Prolapse of the mitral valve was present in seven of 11 patients. There was no relationship between the degree of aortic root enlargement and the presence of prolapse. However, in five of seven patients with prolapse there were premature ventricular contractions recorded during the echocardiogram or on a separate electrocardiogram. In four patients without prolapse, no premature atrial or ventricular contractions were seen.

MARFAN'S SYNDROME is associated with dilatation of the aorta, with aortic insufficiency and with mitral insufficiency secondary to prolapse of the mitral valve.[1] Clinical assessment has been difficult because deformities of the chest wall alter cardiac position, and because of the imprecision of most noninvasive diagnostic techniques. Echocardiography, however, is well suited to evaluate these patients because it can reliably measure dimensions of the aortic root and assess configuration of the aortic and mitral valves. Because it is noninvasive, serial echocardiographic examination may be used to look for evidence of progression of disease. There is a preliminary suggestion that negative inotropic drugs such as propranolol may slow development of dilatation of the aortic root in these patients;[2] hence, echographic monitoring may have therapeutic utility. Some patients with Marfan's syndrome have been noted to have the mitral valve prolapse syndrome described by Barlow and co-workers;[3] an echocardiographic report of such a case has been made.[4] One study found that in 21 of 35 patients with Marfan's syndrome there were dilated aortic roots, and in 32 there was echocardiographic evidence of prolapse of the mitral valve.[5]

These previous echocardiographic reports have not commented on the incidence of arrhythmias in patients with Marfan's syndrome. This study presents echocardiographic findings in 11 patients with skeletal evidence of Marfan's syndrome and notes the frequency of ventricular arrhythmias associated with prolapse of the mitral valve.

Patients and Methods

The 11 patients were from nine families; a definite family history of Marfan's syndrome was obtained in seven of 11. Ten patients with known diagnoses of Marfan's syndrome were referred

From the Department of Medicine, School of Medicine, University of California San Francisco, San Francisco. Dr. Freed is presently at the University of Colorado Medical Center.

Submitted, revised, May 25, 1976.

Dr. Freed was a Fellow in the Division of Clinical Pharmacology and was supported by U.S. Public Heath Service Training Grants GM-00001 and GM-01791. Dr. Schiller is supported in part by School of Medicine Research Evaluation and Allocation Committee, Grant MSC No. 59 (Huntington Fund).

Reprint requests to: Nelson B. Schiller, MD, Department of Medicine, Room C-340, University of California, San Francisco, San Francisco, CA 94143.

for echocardiographic study to the noninvasive cardiology laboratory of the University of California, San Francisco; one patient presented with a primary complaint of palpitations and was discovered at the time of examination to have Marfan's habitus.

Examinations were done with a Picker EV-10 echocardiograph, and echoes were recorded with a Honeywell 1856 strip chart recorder or directly on Polaroid® film. Emphasis was placed on recording the dimension of the aortic root, size of the left atrium, and shape and function of the aortic and mitral valves. The aortic root and left atrium were measured according to the criteria of Brown, Harrison and Popp,[6] who found that in 50 patients without aortic or mitral valve disease the aortic root dimension was 32.7±4.5 mm. In our laboratory, normal aortic root dimension measured similarly is 30±2 mm (range 24 to 35 mm).

The electrocardiogram was recorded simultaneously.

Results

In all adult patients aortic roots were enlarged (greater than 35 mm), with a median dimension in adults of 52 mm (range 36 to 70 mm) (Table 1). In seven patients systolic prolapse of the mitral valve was present. In five of these seven

TABLE 1.—*Echocardiographic Findings in 11 Patients with Marfan's Syndrome*

Patient	*Sex*	*Age*	*Aortic Root Dimension (mm)**	*Left Atrial Size (mm)*	*Mitral Valve Prolapse*	*Rhythm*
1	F	33	68	14	Yes	Premature ventricular contractions
2	F	29	40	24	Yes	Normal
3	M	48	70	25	Yes	Premature ventricular contractions
4	F	7	30	17	No	Normal
5	M	43	48	27	No	Normal
6	F	25	36	21	No	Normal
7	M	34	39	27	Yes	Premature ventricular contractions
8	M	15	47	18	No	Normal
9	F	37	37	32	Yes	Normal
10	M	30	55	41	Yes	Premature ventricular contractions
11	M	18	62	18	Yes	Premature ventricular, premature atrial contractions

*Normal value at this institution is 30 ± 2 mm.

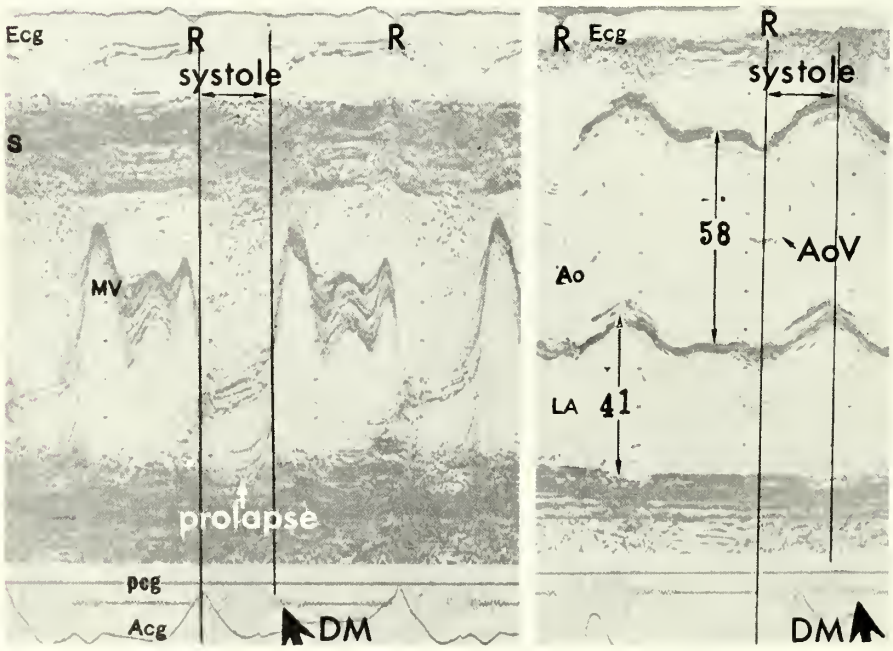

Figure 1.—Echocardiogram of patient 10, a 30-year-old man with Marfan's syndrome. Mitral valve is prolapsed **(left panel)** and aortic root is enlarged **(right panel).** Acg=apex cardiogram, Ao=aorta; AoV=aortic valve, DM=diastolic murmur of aortic insufficiency, LA=left atrium, MV=mitral valve, pcg=phonocardiogram, s=septum.

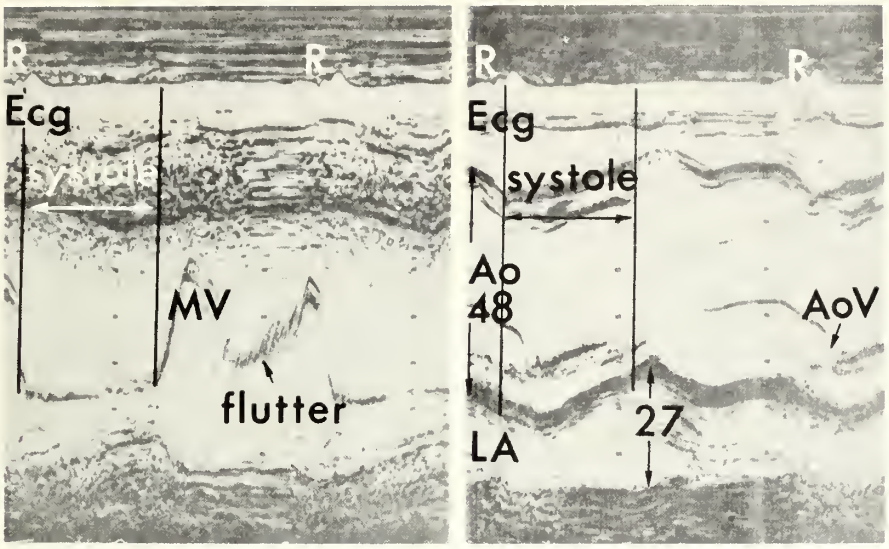

Figure 2.—Echocardiogram of patient 5, a 43-year-old man with Marfan's syndrome. Mitral prolapse is not seen **(left panel)**, although systolic configuration is slightly flatter than expected; note the flutter of aortic insufficiency. Aortic root is moderately enlarged **(right panel)**. Ao=aorta, AoV=aortic valve, LA=left atrium, MV=mitral valve.

there were premature ventricular contractions during echocardiographic examination (which lasted approximately one hour) or during routine electrocardiographic study. We did not note arrhythmias in any patient without prolapse ($X^2 = 2.85$; $.10 > p > .05$). We identified no differences between men and women in incidence of prolapse or degree of dilatation of the aortic root.

The degree of dilatation of the aortic root was not always related to the presence of disease of the mitral valve (Figures 1 through 3). Prolapse was seen with only mild enlargement of the aortic root and was absent in one patient with relatively severe dilatation of the aortic root.

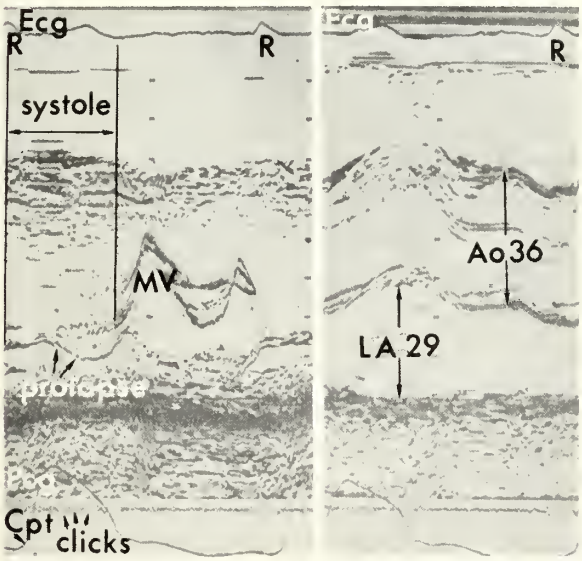

Figure 3.—Echocardiogram of patient 9, a 37-year-old woman with Marfan's syndrome. Mitral valve shows systolic prolapse **(left panel)**, but aortic root is only slightly enlarged **(right panel)**. Phonocardiogram recorded three separate clicks during mid and late systole. Ao=aorta, Cpt=carotid pulse tracing, LA=left atrium, MV=mitral valve, Pcg=phonocardiogram.

Discussion

Marfan's syndrome is a generalized connective tissue disorder with autosomal dominant inheritance. The specific biochemical defect is unknown, but the pathologic process involves disruption of the normal architecture of connective tissue without inflammation. This process is called cystic medial necrosis in the aorta and myxomatous degeneration in the valves of the heart. The disease has variable expression—for example, in the frequency of dislocation of the lens or in the severity of such skeletal abnormalities as pectus carinatum, pectus excavatum and kyphoscoliosis. Although dissection of the aortic root is the most frequent cause of death in these patients, precise evaluation of the status of mitral valves and aortic roots has been limited to those patients for whom angiography could be therapeutically justified.

Echocardiographic examination in our patients with Marfan's syndrome has confirmed the very high incidence of disease of the aortic root and mitral valve that has been reported by others.[5] In all patients there were enlarged aortic roots, and in 64 percent (seven of 11) prolapse of the mitral valve was present. Our findings suggest that premature ventricular contractions are likely to be found in those patients with prolapse. Although arrhythmias have been associated with the mitral valve prolapse syndrome in about 30 percent of patients in whom the syndrome has been identified, a common pathologic link has not

been established.[7,8] Findings in our studies of these patients with Marfan's syndrome suggest a possible etiologic connection in that no arrhythmias were observed when disease was confined to the aortic root, but premature ventricular contractions were observed in five of seven patients in whom there was systolic prolapse of the mitral valve. This observation by itself does not define the cause of the premature beats, but it is compatible with a causal rather than an incidental association between arrhythmia and prolapse.

Serial echocardiographic examinations may have value in the long-term management of patients with Marfan's syndrome. The risk of fatal dissection may be reduced by administration of propranolol, and a study testing this possibility is under way.[2] Progressive enlargement of the aortic root as measured by echocardiogram may prove to be a useful indicator for beginning therapy. Echocardiography may further assist in the monitoring of such treatment.

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Cardiovascular Applications of Nuclear Medicine

Over the past few years two techniques of noninvasive isotopic study of the heart had been extensively tested clinically. The two major areas of application of these techniques are (1) evaluation of regional myocardial perfusion using peripheral venous injection of thallium-201 and (2) identification of acute myocardial infarction with radiopharmaceuticals that accumulate in the infarcted myocardium such as technetium-99m (^{99m}Tc) phosphate compounds.

Thallium-201 behaves as potassium; after injection it accumulates in the normal myocardium as a function of regional myocardial perfusion and of extraction over the cellular membrane by activation of the Na+, K+, adenosinetriphosphatase system. Infarcted myocardium is shown by thallium-201 as an area of notably decreased activity. Another important application of thallium-201 scintigraphy is visualization of transient ischemic myocardium in patients with suspected coronary artery disease.

Using the knowledge that calcium accumulates in irreversibly damaged myocardium, myocardial infarction imaging has been carried out in experimental animals and in humans by means of ^{99m}Tc phosphate compounds. The pattern of acute myocardial infarction is usually localized increase in myocardial uptake of the isotopic compound. The exact mechanism of myocardial accumulation is unknown but it might be related to deposition of calcium in and around the mitochondria in regions of irreversible ischemia. The main clinical application of this technique is the detection of acute infarctions that are difficult to diagnose by standard electrocardiographic and enzymatic methods such as in patients with left bundle branch block, subendocardial myocardial infarction, intraoperative infarction and new infarction adjacent to regions of old myocardial necrosis. The technique can also be used to evaluate the course of an acute infarction.

The above-noted cardiovascular nuclear medicine applications will be reviewed by an outstanding panel of California physicians with an invited guest speaker. The guest speaker will be Dr. James T. Willerson, Associate Professor of Cardiology and Medicine at the University of Texas Health Institute, Dallas, Texas. This presentation will take place on March 5, 1977, from 9 a.m. to 12:00 noon at the CMA Annual Meeting in Anaheim, California; it has Category I approval for Continuing Medical Education purposes.

JORGE FRANCO, MD
Secretary, CMA Section on Nuclear Medicine
San Jose, CA

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Maintenance Hemodialysis in Myeloma Kidney Disease

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Maintenance hemodialysis and chemotherapeutic agents were used in the treatment of seven patients with end-stage myeloma kidney disease. Results indicate that with the use of such therapy life can be prolonged substantially. It appears that patients with myeloma—with or without serious extrarenal complications—are suitable candidates for maintenance hemodialysis and should not be denied the treatment even in the face of systemic neoplasm.

SINCE THE INTRODUCTION of maintenance hemodialysis for treatment of irreversible renal failure by Scribner and his associates in 1969, the presence of uremia has no longer been inevitably followed by death. It is commonly believed that maintenance hemodialysis is not warranted in patients with systemic neoplasm. However, the result of long-term hemodialysis treatment in seven patients with multiple myeloma in our centers since 1967 has been encouraging.

Most patients with multiple myeloma die of infection or renal failure, or both. By prevention and treatment of infections and adequate control of uremia, patients' lives can be prolonged. Prevention of early death by these measures provides the opportunity for judicious use of chemotherapeutic agents for control of underlying neoplasm.

Our first two patients who received inadequate dialysis and aggressive chemotherapy died of profound granulocytopenia and overwhelming infections in less than three months. Remarkable improvement of longevity and overall performance was achieved by adequate dialysis and low dose chemotherapy in the remaining five patients. The data on long-term hemodialysis treatment in multiple myeloma are scanty. We, therefore, report our experience with management of seven patients with this condition.

Patients and Methods

Seven patients with end-stage renal failure secondary to myelomatosis (six men and one woman) have been treated with maintenance hemodialysis in our centers since 1967. The clinical data from these cases are given in Table 1. The diagnosis of multiple myeloma was suspected on clinical grounds and confirmed by the following investigations: test for Bence Jones proteinuria, serum and urine protein electrophoresis and immunoelectrophoresis, x-ray survey of the bones and bone marrow biopsy. Renal biopsy was done in

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two patients. Dialysis was started when blood urea nitrogen (BUN) concentration exceeded 100 mg per 100 ml or uremic symptoms emerged. An external arteriovenous shunt provided the initial means of blood access in all patients. This was revised or replaced by an internal arteriovenous fistula in the event of incorrectable malfunction. Travenol RSP system was used in all patients with ultraflow II Coil dialysers 5M1751 and 5M1753 in patients 1 through 6 and Dow hollow fiber HFK4 dialyser in patient 7.

In patients 1 and 2 dialysis was carried out twice a week and aggressive chemotherapy administered. Dialysis was increased to three times a week (18 hours per week) and chemotherapy was given with extreme caution in the remaining five patients. Lytic lesions of bones causing severe pain or nerve compression were treated with local irradiation in patients 4, 5 and 6. Findings on serial complete blood cell counts were used to determine the interval and the dose of chemotherapeutic agents. A normal protein, 2 grams sodium, 2 grams potassium diet was prescribed. Fluid intake was restricted to limit the weight gain to less than 2 kg between dialyses. Patient 4 was successfully trained for, and transferred to a home dialysis program. Other patients were trained and given increasing participation in their own dialysis in the center. A gross psychological evaluation was made in each patient periodically.

Clinical staging of myeloma at the time of initial presentation was done retrospectively, utilizing the available clinical data as recently described by Durie and Salmon.[1] Since the quantity of M component was not available in every patient, this measure could not be used for staging purposes.

Results

The results of pertinent laboratory findings and retrospective clinical staging of patients on initial evaluation are shown in Table 2. Moderate to severe azotemia and some degree of proteinuria and anemia were present in all patients. X-ray studies of bones showed various lesions in six patients and no detectable abnormality in one. Hypercalcemia was present in three patients in whom there was a serum calcium value of 12 mg per 100 ml or more. This arbitrary level probably underestimates the degree of hypercalcemia in renal failure. Renal biopsy was done in two patients. On histological examination, intratubular lamellated eosinophilic casts were noted surrounded by syncitium of epithelial cells, a feature diagnostic of myeloma kidney disease. The onset of renal failure was rapid in six patients and gradual in one. In five patients there were lambda, and in two patients there were kappa light chains in specimens of urine. Serum protein electrophoresis showed gamma spikes in four patients, beta spike in one and no apparent spike in another. Diffuse hypoglobulinemia was found in

TABLE 1.—*Case Material and Clinical Data*

Patient	*Age, Sex*	*Presenting Manifestation*	*Date Dialysis Started*
1	41 ♂	Flank pain, proteinuria, progressive azotemia	Jan 1967
2	68 ♂	Cervical spine pain, anemia, prostatism, progressive azotemia	Jan 1969
3	46 ♂	Abdominal pain, anemia, progressive azotemia	Sep 1971
4	57 ♂	Lytic lesions of ribs and thoracic spine, anemia, progressive azotemia	Feb 1970
5	42 ♂	Generalized bone pain, hypercalcemia, anemia, hyperglobulinemia	Jan 1973
6	59 ♀	Bone pain and pathologic fractures of ribs, weakness, anemia, slowly progressive azotemia	Jul 1973
7	50 ♂	Proteinuria, renal calcification, rapidly progressive azotemia after intravenous pyelogram	Jul 1974

TABLE 2.—*Laboratory Data and Clinical Staging*

Patient	*Hemoglobin gm/100 ml*	*Leukocyte Count*	*Serum Calcium mg/100 ml*	*Serum Albumin gm/100 ml*	**Degree of Bone Lesions*	*Serum Protein Abnormalities*	*Urinary Proteins*	*Serum Creatinine*	*Stage*
1	12.2	9,500	12.4	4.4	2+	γ Spike moderate	λ light chains	4.5	3B
2	9.1	7,500	8.8	3.5	1+	β Spike small	λ light chains	9.0	2B
3	9.6	5,100	11.6	4.3	1+	γ Spike small	κ light chains	7.8	2B
4	10.6	11,200	9.0	3.8	2+	No apparent spikes	λ light chains	23.0	2B
5	5.8	4,300	12.2	3.5	3+	γ Spike IgA >1,000 mg	κ light chains	10.3	3B
6	9.4	8,200†	12.6	2.8	2+	Diffuse hypoglobulinemia	λ light chains	8.9	3B
7	8.8	9,500	10.0	3.0	0	γ Spike	λ light chains	8.9	2B

*Extent of bone lesions graded on a scale of 0-3. Normal bone survey (0), osteoporosis (1), lytic lesions (2), extensive destruction and pathologic features (3).
†3 percent plasma cells.

one subject. Bone marrow biopsy was done in all patients and showed atypical plasma cells constituting 10 to 60 percent of cellular elements.

Three patients were found to have stage 3, and four patients stage 2 myeloma on initial evaluation. This was based on the degree of anemia, the extent of bone lesions, and presence or absence of hypercalcemia. All patients belonged to subgroup *B* because there was advanced renal failure in all of them.

The incidence of complications related to vascular access in this group was not different from the rest of our dialysis population. In all patients there was a moderate to severe degree of depression and denial at the onset of dialysis, but pronounced improvement of psychological status was the rule with alleviation of uremia and myeloma-related symptoms after institution of dialysis and chemotherapy. The degree of rehabilitation was quite satisfactory in most of the patients. In no case did renal function improve with dialysis and chemotherapy. Gradual progression of skeletal lesions was shown on serial x-ray studies of bones. The average hematocrit and blood transfusion requirements in the last four patients are shown in Table 3.

TABLE 3.—*Average Hematocrit and Transfusion Requirement*

Patient	*Average Hematocrit (percent)*	*Average Transfusion Requirement/Month*
4	18	1 unit
5	17	2 units
6	21	1 unit
7	24	0.25 unit

Patients 1 and 2 died from granulocytopenia and overwhelming infection in less than three months. This was attributed to inadequate dialysis and aggressive chemotherapy. By increasing the duration and frequency of dialysis, and assuming a less aggressive attitude with respect to chemotherapy, a pronounced improvement in survival rate and morbidity was achieved in the remaining patients. Summaries of dialysis and chemotherapeutic programs and patients' survival on dialysis are shown in Table 4. Patient 3, a Filipino national, did extremely well for six months; he then elected to return to his homeland where he died of inadequate dialysis two months later. Patient 4 lived 36 months on dialysis, 30 months of which were productive and comfortable despite significant bone involvement. Over the ensuing six months he became severely disabled from advanced generalized bone lesions and collapse of cervical vertebrae, resulting in death. Patients 5 and 7 are still alive and relatively active and comfortable 40 and 20 months after initiation of hemodialysis. Patient 6 was transferred to an outside facility where dialysis and chemotherapy were continued. She did well for 12 months, subsequently she became depressed and refused dialysis and died of uremia (Table 4).

Discussion

Multiple myeloma results in a wide variety of renal complications.[2] These renal complications account for 1.6 to 2 percent of all renal disorders requiring admission to hospital.[3,4] Renal failure is the second most common cause of death in cases of multiple myeloma, accounting for 40 percent

TABLE 4.—*Dialysis, Chemotherapeutic and Survival Data*

Patient	*Number Dialysis Per Week*	*Number Months on Dialysis*	*Average Dose and Nature of Chemotherapeutic Agent*	*Number Months on Chemotherapy*	*Patient's Outcome*
1	2	2.5	Cyclophosphamide-200 mg/day; prednisone-60 mg/day	1	Persistent granulocytopenia, penumonia and sepsis resulting in death
2	2	3	Cyclophosphamide-200 mg/day; prednisone-60 mg/day	1.5	Agranulocytosis, pneumonia, sepsis resulting in death
3	3	6	Melphelan-1 mg every other day	6	Moved back to the Philippines where he died of inadequate dialysis 2 months later
4	3	36	Intermittent small doses of melphelan and prednisone + local irradiation	36	Died of collapsed cervical vertebrae
5	3	40	Melphelan-1-2 mg every 2-7 days; local irradiation	40	Alive, active and relatively comfortable
6	3	12	Melphelan-1 mg every 1-3 days	12	Did well for 12 months, subsequently refused dialysis and died of uremia
7	3	20	Cyclophosphamide-500 mg intravenously every 1-3 months	20	Alive, comfortable, retired

of mortality in patients with myeloma,[5] pneumonia being the most common. The median survival declines significantly with development of renal failure in multiple myeloma. Three months survival is less than 30 percent when blood urea nitrogen level equals or exceeds 60 mg per 100 ml.[6] Peritoneal and hemodialyses have been used for treatment of acute reversible renal failure in these patients.[7-9] However, the information on the use of maintenance hemodialysis in multiple myeloma is scanty. The only available report in the literature is that of Leech and co-workers,[10] who reported the result of maintenance hemodialysis treatment in two patients with multiple myeloma in whom renal failure was the only major complication of the disease. One lived 24 months and the other for 10 months on maintenance dialysis. This was well beyond the median survival of such patients. The authors concluded that maintenance dialysis should be considered in those patients with multiple myeloma whose only disability is renal failure. In our series, five of seven patients had significant bone involvement, three had stage 3B and the remaining four stage 2B myeloma at the time of their initial evaluation (Tables 1 and 2), indicating more advanced disease. Our last four patients, who were treated with adequate dialysis and low dose chemotherapy, have done surprisingly well in spite of extrarenal complications and advanced myelomatosis.

In our experience, aggressive chemotherapy is poorly tolerated by myeloma patients with renal failure as evidenced by poor outcome in the first two patients. Adequate dialysis reduces the magnitude of azotemia, thereby improving tolerance to chemotherapy and diminishing the likelihood of irreversible bone marrow suppression and subsequent overwhelming infection. It is probable that the prolongation of life is a result of preventing death from renal failure and severe infection, the two most common causes of death in myeloma. Since chemotherapy in full doses could not be administered and bone lesions gradually progressed in most patients, one may question the contribution of chemotherapy to the prolongation of patients' survival. However, the argument could be raised that the underlying neoplasm may progress faster with no chemotherapy. Further evaluation is necessary to resolve the question.

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Adjuvant Treatment of Colorectal Cancer

A Review

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Surgical operation remains the most effective method of treatment for patients with cancer of the large bowel. However, innovative surgical techniques have not improved survival rates for colorectal cancer in 25 years.

Attempts at increasing survival with chemotherapy as an adjunct to surgical procedures remain inconclusive and controversial. Many adjuvant chemotherapy trials have failed to recognize those prognostic factors—such as nodal involvement, serosal penetration, vascular or perineural invasion, and microscopic invasion at margins of resection—that characterize certain patients at high risk for recurrent cancer. Failure to include only high risk patients in adjuvant chemotherapy is, in part, responsible for the lackluster performance to date.

For rectal cancer, preoperative irradiation increases the chances of cure with surgical operation by reduction of pathologic staging, but it has not increased survival in patients with persistent nodal involvement.

Immunotherapy is a possibly valuable method of treatment; however, it is clinically untested. An adjuvant immunotherapy protocol for high risk patients is described.

THE ONLY ACCEPTABLE curative therapy for invasive adenocarcinoma of the large bowel continues to be radical surgical excision.[1] Unfortunately newer surgical techniques and manipulations have not improved five-year survival rates for more than two decades.[2] Previous attempts to prolong survival by employing radiation (excluding perhaps preoperative irradiation for rectal cancer) and chemotherapy, either as preoperative or as postsurgical adjuvants, have not yet been successful. It is now believed that adjuvant therapies may be effective in subgroups of patients defined by the presence or absence of risk factors. If so, the role of immunomanipulation also holds promise of significance. This paper summarizes previous adjuvant approaches for treatment of large bowel cancer in order to crystallize the rationale for adjuvant therapy including immunomanipulation.

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ABBREVIATIONS USED IN TEXT

BCG = bacille Calmette Guérin
CMI = cell-mediated immunity
COG = Central Oncology Group
5-FU = 5-fluorouracil
Me-CCNU = 1-(2-chlorethyl-3-4 methylcyclohexyl)-1-nitrosourea
MER = methanol extracted residue of BCG
VASAG = Veterans Administration Surgical Adjuvant Group
WCSG = Western Cancer Study Group

Adjuvant Radiation Therapy in Rectal Cancer

Radiation therapy for patients with unresectable primary large bowel cancer or a local recurrence has been shown to have significant palliative effects.[3,4] It has been postulated that preoperative irradiation to rectal and low sigmoid cancer would improve chances of survival.[5-7] A retrospective survival study of 1,700 previously untreated patients with rectal cancer has been reported from Memorial Hospital in New York. With the use of preoperative radiation therapy there was a significant increase in the five-year survival rate (37 percent) over that for surgical procedures alone (23 percent) in patients who had lymph node involvement only.[1,8-10] Results of a partially randomized prospective study subsequently showed that in cases of lymph node involvement treated with surgical operation alone there was a slightly increased proportion of patients surviving five years, compared with survival when both radiation therapy and surgical operation were used.[1,11,12]

Several reviews of the Veterans Administration Surgical Adjuvant Group's (VASAG) preoperative radiation protocol for rectal cancer show a 12 percent increase in five-year survival in only those patients receiving both radiation therapy and abdominoperineal resection. Concurrent randomized controls treated only surgically were used in these studies.[13-16] Preoperative irradiation was given in doses of 2,000 to 2,500 rads during two weeks. The current VASAG preoperative radiation therapy protocol utilizes 3,150 rads in 18 fractions randomly matched against no preoperative treatment.

The Central Oncology Group (COG) and the Radiation Therapy Oncology Group are conducting a study (COG No. 7240) comparing high (4,000-4,600 rads in four to five weeks) and low dose (2,000-2,500 rads in two weeks) preoperative radiation therapy in rectal cancer. Results in both groups of patients will be compared with findings in a group that received no preoperative treatment.

The European Organization for Research on Treatment of Cancer recommends use of 3,450 rads preoperatively over a 18-day period for rectal cancer. A comparison is being made with preoperative irradiation plus chemotherapy with 5-fluorouracil (5-FU).[15]

The above-cited studies permit certain conclusions concerning preoperative radiation therapy in rectal cancer: (1) Preoperative rectal irradiation reduces the frequency of lymph node involvement by about 13 percent.[13-16] By reducing pathologic stage, radiation therapy appears to increase chances of surgical cure even when low dose irradiation is used. (2) Preoperative rectal irradiation reduces local recurrence, regardless of pathologic staging.[15] (3) However, no randomized study has yet shown a survival benefit with preoperative radiation in patients in whom there continues to be nodal involvement at the time of operation.

Factors Associated with Poor Prognosis in Large Bowel Cancer

One of the pitfalls that plagued earlier surgical adjuvant chemotherapy trials was a lack of awareness of those patient characteristics associated with a high probability of disease recurrence, regardless of the adequacy of the surgical resection.

Pathologic stage of the tumor has been shown to be a major prognostic factor according to Dukes:[17]

A—Cases in which the tumor has not penetrated the muscle wall of the bowel;
B—Cases in which tumor extends to the pericolic or perirectal tissues but has not reached the lymph nodes;
C—Cases in which tumor has metastasized to the proximal (C_1) or regional (C_2) lymph nodes, and
D—Cases in which tumor has metastasized to distant locations.

Survival at five years is:[18]

Dukes' *A*—60 percent to 80 percent;
Dukes' *B*—25 percent to 65 percent;
Dukes' *C*—6 percent to 28 percent;
Dukes' *D* involving liver or lung—less than 15 percent.

In addition to Dukes' staging, other poor prognostic indicators are:

- Presence of gross or microscopic blood vessel invasion in the resected primary specimen has been associated with 19 to 37 percent five-year survival.[19-21] In patients with vascular invasion, the probability of recurrent tumor is 74 percent.[22]
- Perineural involvement in the resected surgical specimen has been related to a 20 percent five-year patient survival.[21]
- Any combination of lymph node, vascular or perineural tumor infiltration has additive effects in terms of decreasing the chances of a five-year survival.[21]
- An exceedingly high rate of anastamotic recurrence is observed in patients in whom resection margins are not free of microscopic tumor foci.

In one review, first disease recurrence within 18 months of surgical operation was observed in more than 75 percent of patients in whom one of the above poor prognostic factors was seen.[23]

Adjuvant Chemotherapy

Historically, adjuvant chemotherapy was used in an attempt to destroy cells left in the operative field and to prevent spread via the blood stream or lymphatics during surgical operation. Therefore, early studies employed short duration adjuvant therapy to irradicate the small pool of locally residual cancer cells. At first, local irrigation of the bowel ends with half-strength Dakin's solution or 1:500 perchloride of mercury was advocated.[24-28]

Systemic chemotherapy began with early randomized controlled studies testing effects of triethylenethiophosphoramide (thiotepa) and fluorodeoxyuridine (FUDR). Various routes of administration were used (intraperitoneal, mesenteric vein, intravenous) but were unsuccessful.[29-31]

Increased survival in patients with lymph node involvement was shown, compared with a retrospective control group not treated, when intraluminally given 5-FU and systemic administration of 5-FU two days postoperatively were used.[32] These observations have motivated the initiation of a randomized cooperative clinical study comparing results of intraluminally given 5-FU in combination with systemic administration of 5-FU after surgical operation with results of operation alone.[33]

In 1971 the VASAG reported on a randomized study of no treatment compared with 5-FU treated colon cancer patients.[34] 5-FU was given in the immediate postoperative period (14 days postresection) for five successive days at 12 mg per kg of body weight intravenously. Treatment assignment was not stratified by Dukes' classification or other prognostic variables influencing disease recurrence, but by the surgeon's opinion regarding potential for cure. All patients were followed for survival. Those patients who received surgical procedures termed "clinically palliative" and "clinically curative" received a second course of 5-FU six weeks later. There was no statistically significant difference in the five-year survival rate or the disease-free interval between treated and untreated populations in any of the patient groups. Furthermore, retrospective analysis by Dukes' classification again failed to show that therapy with 5-FU achieved survival rates superior to those of control populations. The five-year survival rate for patients (308) undergoing "curative resection" was 58.5 percent for treated patients (142) versus 49.4 percent for control patients (166). The trend of this study appears to favor 5-FU treatment, but statistical significance is lacking.[35] Thus, findings in early trials utilizing thiotepa, FUDR and 5-FU have failed to show significant prolongation in survival. Doses, schedules, route of administration, the short duration of adjuvant treatment and disregard for prognostic factors in treatment assignment may be important factors in this failure.

The advocation of prolonged intermittent systemic adjuvant chemotherapy came about with the realization that (1) occult metastatic cancer sites can exist at the time of surgical operation and do not result exclusively from surgical manipulation and (2) repeated courses of treatment are necessary to irradicate this small residual tumor cell burden.

Prolonged intermittent 5-FU adjuvant therapy is being tested in a randomized prospective study by the Central Oncology Group.[36] Before random assignment to groups receiving adjuvant 5-FU therapy or no treatment, patients with poor prognosis are classified as "curative" or "palliative" resection. Poor prognosis in the curative group includes the following factors: (1) positive lymph nodes, (2) serosal penetration or invasion of perirectal fat, (3) blood vessel invasion, (4) lymphatic invasion and (5) cancer in other organs removed as part of the resection.

In this study, 5-FU was given intravenously at 12 mg per kg of body weight per day for four days and then 6 mg per kg of body weight every other day for five doses or to toxicity. Following

this induction course, 5-FU was given weekly at 12 mg per kg of body weight for one year. Endpoints were first disease recurrence and death.

The follow-up period is still relatively short but at last report 49 of 64 patients (77 percent) classified as "curative" resection were disease-free after treatment with 5-FU, as compared with 42 of 63 patients (67 percent) similarly classified and assigned to no treatment.[36] For both curative and palliative resected patients 5-FU treatment has not shown significant superiority over no treatment with respect to disease-free interval or five-year survival.

The VASAG has also investigated prolonged intermittent chemotherapy (5-FU) in colon cancer. Chemotherapy was given in the same manner as in their previous study[34] but was repeated every six weeks for 18 months. Case accrual terminated in August 1973. To date, no difference has been shown in patient survival associated with prolonged 5-FU treatment.[35]

Lawrence has recently reported no significant treatment benefit, regardless of stage, with 5-FU used as a prolonged intermittent postoperative (one year) adjuvant in colorectal cancer patients. Treatment benefit was measured in terms of disease-free interval and survival.[37]

Other nonrandomized studies showing significant superiority of 5-FU over no treatment continue to be reported in the literature.[38] The success of adjuvant 5-FU chemotherapy in prolonging patient survival can not be determined by retrospective comparison with control populations.

The recent reports of higher than anticipated regression proportions in metastatic colon cancer when drugs with low individual activity are combined have prompted these drug combinations to be considered as adjuncts to surgical operation.[39-42] The use of combination chemotherapy as adjuncts to surgical operation adds further risk of systemic toxicity, difficult patient management, interference with patient quality of life and potentially greater immune "paralysis" (tolerance) to residual tumor burden. In spite of these potential difficulties, several cooperative groups have initiated studies using combination chemotherapy (namely Me-CCNU [that is, 1-(2-chlorethyl-3-4 methylcyclohexyl)-1-nitrosourea] plus 5-FU) as an adjunct to surgical operation.

Immunotherapy as Adjuvant Treatment

Many investigators have theorized the clinical use of immunomanipulation may be effective only at the time of minimal tumor burden because host immune "paralysis" increases with increasing tumor burden.[43] Reactive regional lymph node hyperplasia with germinal center proliferation draining a primary malignancy has been observed in both breast and colon cancer.[44-47] This suggests a host immune response to the tumor. Postoperative irradiation of regional draining lymph nodes in breast cancer has been a common practice and now has been associated with decreased survival when compared with nonirradiated postoperative controls.[48] This disturbing observation perhaps reflects the result of lymph node destruction secondary to radiation therapy, thus "paralyzing" an important defense against dissemination. It is conceivable that chemotherapy may act similarly to cause both regional and systemic lymph node immunosuppression and permit enhanced tumor growth.

Implementation of nonspecific immunotherapy at the time of minimal tumor burden will theoretically stimulate cell-mediated immunity (CMI) and increase the intensity of low level antitumor immune responses leading to tumor rejection. The cells involved in this CMI anticancer effect include macrophages, lymphocytes, polymorphonuclear leukocytes and, to some extent, plasma cells. Some or all of these cell types may be stimulated by various immunotherapies. The degree of cellular response often depends on route of drug administration. In animal tumor systems the immunostimulants, Corynebacterium parvum or bacille Calmette Guérin (BCG) appear to have greater immunocytotoxicity to a cancer inoculum when given intravenously or intraperitoneally, as compared with subcutaneous administration.[49,50] It is postulated from animal data that the intravenous route is superior to the subcutaneous route because of direct visceral systemic stimulation by intravenous delivery rather than the regional lymph node hyperplasia which follows subcutaneous administration.

A randomized surgical adjuvant protocol for patients with colorectal cancer who have had "curative" surgical resections and in whom any one of the poor prognostic factors listed above is present has been designed by the Western Cancer Study Group (WCSG). The agents employed are immunostimulants: Corynebacterium parvum and levamisole. The WCSG chose C. parvum for several reasons: (1) It appears to be a potent anticancer immunostimulant in many animal tumors and even more effective than BCG in

identical immunoadjuvant animal tumor systems;[51,52] (2) C. parvum is formalin-fixed and not capable of transmitting active disease as is BCG, nor is it dependent on viable organisms for its immunostimulant properties, as is BCG; (3) C. parvum is not plagued with variation in organism viability within intrainstitutional and interinstitutional manufacturers, as is BCG; (4) C. parvum preparation does not show inconsistent dosage administration caused by cellular clumping within multidose vials as has been the case with BCG;[53] (5) in Phase II clinical trials, C. parvum has shown single agent antitumor effect in several metastatic tumor types.[54]

C. parvum toxicity has been established in Phase I trials. Side effects include pain at injection site, fever, malaise, flu-like syndrome and sensitivity to barbiturates when given subcutaneously.[55] In addition, severe chills, fever, hypotension and hypertension may be observed when the agent is administered intravenously.[56] Pain at subcutaneous injection sites can be obviated by mixing with xylocaine. Side effects tend to be more severe when C. parvum is given intravenously compared with subcutaneous injection.[57,58] The high fevers and chills are associated with large intravenous doses and are most severe with the first intravenous injection, diminishing with subsequent doses.[57,59] If initial intravenous doses are kept small and subsequent doses are slowly increased, these toxic effects diminish.[57,60]

Levamisole, an established antihelminthic, was discovered by Renoux and Renoux to possess immunostimulating properties in animals.[61] Since their initial work, many animal data have accumulated to confirm and extend these observations.[62] In human studies levamisole has been found to restore recall skin test antigens, and to increase *in vitro* lymphocyte reactivity.[63,64] In general, it appears that levamisole increases a low level of preexisting immunity rather than stimulating an immune response de novo. The mechanism by which this occurs may be macrophage stimulation via a serum factor (which is not the drug) found in levamisole-treated patients.[65] Although its performance as an antitumor agent in animal models appears to be less than C. parvum or BCG, findings in recent adjuvant studies by Rojas in patients with breast cancer and Amery in patients with lung cancer have shown increased disease-free intervals in these patients when compared with a randomized prospective treatment control group.[66,67] Such preliminary reports are exciting but remain to be clinically confirmed. When given as discontinuous therapy (that is, three days of oral administration every two weeks) side effects occur in about 5 percent of patients. They include central nervous system stimulation manifested by nervousness and insomnia; gastrointestinal complaints, such as nausea and vomiting, and skin rash. There has been no adverse effect on liver, kidneys or cardiac function recorded.

Further discussion of current information on other promising nonspecific immunostimulants such as BCG and methanol extracted residue of BCG (MER) is beyond the scope of this article. However, recent preliminary results have shown increased disease free interval for BCG treated colon cancer patients (Dukes' *C* stage) compared with historical controls. Even though historical controls have been used for treatment comparison such data help substantiate early implementation of immunotherapy in cancer of the large bowel.[68] Clinical trials of specific immunotherapy (for example, with transfer factor, immune ribonucleic acid (RNA), modified tumor antigens, cell wall extracts) are chiefly limited to single institution studies with small numbers of patients because of the large procurement and logistic problems.

Proposed Immunoadjuvant Trials for Colon Cancer

Several cooperative group studies that will use both chemotherapy and immunotherapy in combination are presently undergoing development and activation. The Large Bowel Cancer Working Group has a protocol proposal prepared by Holyoke at Roswell Park Memorial Institute for "curative" postsurgical patients with adenocarcinoma of the colon. In this study there is randomization to four treatment arms: (1) control; (2) 5-FU plus Me-CCNU; (3) MER alone; (4) 5-FU plus Me-CCNU and MER. The VASAG has amended their current colon adjuvant protocol No. 27 for patients with histologically proven residual disease. These patients will be randomized to prolonged intermittent chemotherapy (5-FU plus Me-CCNU) with or without MER. Further details concerning these proposals are not available.

The Western Cancer Study Group has elected not to combine chemotherapy and immunotherapy in a surgical adjuvant study for colon cancer. This is based on several reasons: (1) there are no conclusive data that single or combi-

nation adjuvant chemotherapy prolongs disease-free interval or survival for large bowel cancer; (2) chemotherapy may entail additional systemic toxicity and potential for impairment of quality of life; (3) while chemotherapy may enhance host immunoreactivity to large volume malignancies, it also may "paralyze" established nodal defense systems against minimal tumor cell numbers; (4) combination chemotherapy when used in an adjuvant setting leaves few alternative chemotherapeutic drugs available at first disease recurrence; (5) chemotherapy could potentially be antagonistic to immunomanipulation; (6) information about dose, routes of administration and single agent effectiveness for immunostimulants should be established before combination with chemotherapeutic regimens.

The WCSG study employs immunotherapy only for adjuvant treatment of patients with totally resected colorectal carcinoma and poor prognostic indicators. The patients will be randomized to: placebo; levamisole; C. parvum given subcutaneously; C. parvum given intravenously. Disease-free interval, survival and side effects will be the endpoints of treatment effectiveness.

As in any large scale study assessing the effectiveness of adjuvant therapy, case accrual is a critical aspect. A study designed for long-term follow-up must encourage rapid case accrual. The WCSG invites any interested physicians seeking further information concerning this study and possible case referral to contact the authors. The WCSG is a multiinstitutional cooperative cancer study group with investigators throughout the western United States. Participating WCSG investigators are very willing to assist physicians in their area who have potential patients to enroll.

Summary

An historical review of early treatment of large bowel cancer is presented. Several observations concerning the efficacy of single modality therapy can be made with regard to improving survival. (1) Since newer surgical techniques have not altered survival rates in 25 years, it appears that further surgical manipulation is unlikely to achieve future survival benefit. (2) Preoperative radiation therapy for rectal cancer both improves surgical curability by reducing pathological stage and reduces local recurrence; but it has not resulted in increased survival in patients with persistent nodal disease. (3) Short-term adjuvant chemotherapy is of no apparent value in increasing survival; prolonged intermittent adjuvant chemotherapy has not yet achieved increased survival. The use of combination chemotherapy as an adjunct to surgical operation is currently being evaluated and no data as to its efficacy are available. (4) The employment of immunotherapy as an adjunct to surgical operation is theoretically sound but clinically untested. Immunotherapy as proposed by the WCSG is described. If immunotherapy, chemotherapy or radiation therapy are proved to be effective in increasing survival in large bowel cancer then ultimately a multimodality approach may be adapted to further influence disease curability.

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Immunotherapy of Cancer

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Clinical studies have indicated a close relationship between immunological competency and the growth of human cancer. Studies in animal systems have indicated that immunological mechanisms are important in host-tumor existence. A number of agents are in the process of being evaluated for their immunotherapeutic potential in patients with cancer. These include levamisole, bacille Calmette Guérin (BCG) and Corynebacterium parvum. While the precise role of these agents in the treatment of human malignancy remains to be clearly defined, they do appear to be useful as adjuncts to other forms of cancer therapy such as radiation therapy, chemotherapy and surgical operation.

THE CONCEPT that both human and animal neoplasms contain antigens against which the host is capable of reacting immunologically is not new. The advances in the immunology of infectious diseases at the turn of the century prompted an intense investigation into the applicability of immunizations to protect against cancer. However, the lack of highly inbred strains of animals prevented the investigation of tumor specific antigens. Without these inbred animals it was impossible to distinguish between histocompatability antigens carried in the tumor cells from tumor specific antigens.

The concept of tumor immunology was largely ignored until 1943 when Gross was able to immunize mice against a sarcoma induced by methylcholanthrene arising within an inbred strain of mice.[1] It remained for Phren and Main in 1957 to definitively show the presence of tumor specific transplantation antigens in carcinogen induced murine tumors.[2] These studies established tumor immunology as a legitimate concept and since 1957 there has been a virtual explosion of work in animal and human tumor immunology.

Tumor antigens have been identified by a variety of different techniques in animal neoplasms induced by both viruses and chemical agents. In view of this evidence in animal neoplasms it was logical to assume that human neoplasms also contained cancer specific antigens similar to those found in animal tumors. This rationale is supported by some rather impressive clinical observations which indicate the importance of host-tumor defense mechanisms:

- It is clear that under certain conditions spontaneous regression of malignancy does occur. Reports of spontaneous remission of proven malignant tumors have been well substantiated.

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ABBREVIATIONS USED IN TEXT
BCG = bacille Calmette Guérin
RNA = ribonucleic acid

Hypernephroma, melanoma, neuroblastoma and choriocarcinoma are the major types of tumors that most frequently regress spontaneously.[3]

• Cancer cells have been found repeatedly in the systemic venous blood in a high percentage of patients during surgical operation. The presence or absence of these tumor cells in the blood, or in wound washings at the time of operation or following operation, does not correlate with survival. This observation suggests that host factors are important in preventing the growth of these circulating tumor cells.

• The development of rapidly progressive, recurrent disease 10 to 20 years after control of the primary tumor is also indicative of the presence of host-tumor defense mechanisms.

• Another compelling clinical observation is that patients with depressed immune responses have an increased risk of developing cancer.[4] Children with congenital immune deficiency syndromes have a very high incidence of cancer at any early age. In addition, malignant conditions are apt to occur in transplant recipients who are receiving immunosuppressive agents. These observations, along with the observations that cancer patients with a general depression in their immune reactivity, have more rapidly growing neoplasms and a poorer prognosis following surgical therapy strongly[5] indicates that immunological mechanisms are important in the host-tumor relationship.

There has been considerable laboratory evidence to corroborate these clinical observations. These studies have clearly shown the presence of tumor associated antigens in human tumors and indicate that the host responds immunologically to these antigens. A variety of *in vitro* techniques have been employed to identify these antigens including immunofluorescence, colony inhibition, complement fixation, immunodiffusion, lymphocyte mediated cytotoxicity, lymphocyte blastogenesis and various radioimmunoassays. These *in vitro* assays not infrequently show evidence of tumor immunity in patients with progressive disease. The explanation for this may be the presence of circulating soluble substances that appear to interfere or block certain immunological reactions directed toward tumor antigens.[6] These studies, as well as studies in animal systems, have suggested the importance of the immune response in human cancer, and it seems reasonable that these principles of tumor immunology be applied to the treatment of cancer.

Immunotherapy

Immunotherapy can take one of several forms. These can be grouped under the following classifications:

• *Nonspecific immunotherapy* involves stimulation of the immune system with adjuvants that have the ability to nonspecifically enhance a patient's capacity to respond to his own tumor.

• *Active specific immunotherapy* involves the active stimulation of the immune system with tumor vaccines in an attempt to induce specific autoimmunity against cancer specific antigens. These vaccines can take the form of whole tumor cells or fractions of tumor cells.

• *Passive or adoptive immunotherapy* involves the administration of antisera, immune lymphoid cells or subcellular fractions from another host which has been specifically immunized against cancer specific antigens.

By far the most extensive experience with these different modalities has been with active nonspecific and specific immunotherapy. Adoptive or passive immunotherapy has been employed, but to a much lesser extent.

Passive or Adoptive Immunotherapy

Theoretically, passive or adoptive immunotherapy can be employed with the use of humoral antibodies, or cell mediated immune factors. Therefore, this form of immunotherapy may employ the administration of serum or lymphoid cells, or fractions of lymphoid cells. Since the accumulated evidence suggests that tumor immune destruction is mediated by cellular immune mechanisms, most of the attention directed toward adoptive immunotherapy has centered around cellular immune mechanisms. Some clinical studies have been done using humoral antibodies, but results of these have largely been inconclusive. Indeed, certain observations suggest that humoral antibody may have an adverse effect on the tumor-host relationship. Passive immunotherapy with antisera produced in a foreign species has been attempted. However, such antitumor sera have proved very toxic in the recipient because they contain antibodies against the normal

tissues of the recipient. Other sources, such as from patients who have been cured of the malignancies and in whom there are high titers of cytotoxic antibody, also may be used. A comprehensive review of the serotherapy of malignant disease has recently been published.[7]

The possibility of adoptive immunotherapy using lymphoid cells or fractions of lymphoid cells has stimulated a great deal of interest. In animal studies with highly inbred laboratory animals, experiments have indicated that transferred lymphocytes that persist in the host have a significant immunotherapeutic effect.[8] However, this is difficult to apply in a clinic because of the difficulty of rejection of the transferred lymphocytes due to HL-A differences between the donor and the recipient. Several studies have been done attempting to induce remissions in cancer patients with lymphocytes from patients in whom there previously has been a complete clinical remission.[9] These studies have not been universally successful and certain logistical problems at present make this a very difficult form of immunotherapy.

The use of extracts from lymphoid cells is particularly attractive because these extracts do not contain HL-A specificities, and therefore are not rejected by the recipient. The most promising subcellular materials are immune ribonucleic acid (RNA)[10,11] and transfer factor.[12,13] Immune RNA is information RNA that is extracted from the lymphoid organs of specifically sensitized donors. This immune RNA is capable of transferring immunologic capabilities to unsensitized lymphocytes. Human tumors are used to immunize a heterologous species, such as sheep, and RNA extracted from the sheeps' lymph nodes is used for immunotherapy. Immune RNA generated in this fashion is capable of transferring to normal lymphocytes the ability to kill tumor cells *in vitro*. In essence, the immune RNA instructs the lymphocytes to destroy the tumor cells. There are a number of trials that are now evaluating the effect of immune RNA in a variety of human neoplasms.[11] At present it is clear that immune RNA is well tolerated in humans; however, the results of these clinical trials are too preliminary for conclusions to be drawn from them.

Transfer factor is another agent capable of transferring immunity from one human to another.[12,13] Transfer factor extracted from leukocytes from one human is capable of transferring immunity to skin grafts and tuberculosis and a variety of other antigens. Transfer factor is very easy to prepare, it is well tolerated and it contains no HL-A antigens against which the recipient can react. Transfer factor has been used in a variety of clinical trials including studies with malignant melanoma, breast cancer, renal cell carcinoma and sarcoma.[13] Some impressive results have been reported using this method of immunotherapy and sufficient information has been generated to set up prospective trials evaluating transfer factor. At present several institutions in the United States are evaluating transfer factor as an adjuvant to surgical operation in patients with sarcomas. These studies are not of sufficient duration to draw any concrete conclusions.

Active Nonspecific and Specific Immunotherapy

There are a variety of agents capable of a nonspecific immune stimulation. These agents enhance antibody formation to a variety of different antigens, they nonspecifically enhance cellular immunity and they may stimulate macrophage function. Many of these nonspecific stimulators have been evaluated but BCG, Corynebacterium parvum and levamisole have received the greatest attention and the most thorough evaluation. For these reasons, this discussion will focus on these nonspecific immunostimulators.

BCG

Old[14] and Halpern[15] showed several years ago that BCG has significant antitumor activity against a wide variety of animal neoplasms. In animals a single injection of BCG results in enhanced humoral immunity, increase in macrophage function, increased resistance to bacterial infection, accelerated homograft rejection and increased resistance to tumor challenge.[16] Results of animal and clinical studies have indicated that local tumor control is most readily achieved by the direct intralesional injection of BCG into cutaneous tumor nodules. Also, the direct local injection of BCG into the neoplasm is the best way to stimulate systemic tumor immunity. This antitumor effect of BCG is abrogated by pretreatment with antilymphocyte serum, and with cortisone. In addition, it is ineffective in thymectomized mice. This evidence and experience in human studies indicate, therefore, that an immunocompetent host is necessary for BCG to be effective.[17]

The second most effective immunizing technique is with BCG mixed with tumor cells and in-

jected intradermally in an area that drains to the regional lymph nodes that drain the tumor being treated. BCG is least effective when given at sites distant from the tumor.[18] Animal and clinical studies have indicated that BCG immunotherapy is effective against a limited amount of disease. For instance, in certain animal leukemia models BCG appears to be effective against only 10^5 cells. Since this form of immunotherapy is known to be effective against a limited amount of disease, it is generally felt that it should be used in combination with a major cytoreductive modality such as surgical operation, radiation therapy or chemotherapy.

Clinical experience with BCG as an intralesional immunotherapeutic agent in patients with cutaneous melanoma[17] indicates that BCG is most effective in patients who are immunocompetent as determined by their ability to express delayed cutaneous hypersensitivity to antigens such as tuberculin purified protein derivative and 2-4-dinitrochlorobenzene. When injected directly into intradermal melanoma deposits, BCG vaccine has induced complete remission of the injected tumor in 90 percent of immunocompetent patients. In addition, in 15 to 20 percent of these patients there also was regression of uninjected melanoma nodules indicating that in some cases the effect was not limited to the injection site. It should be emphasized that intralesional administration of BCG is most effective against intradermal deposits. Subcutaneous and visceral metastases do not respond as well. Patients who are anergic respond poorly to intralesional injection, and uninjected nodules in these patients never regress. Intralesional BCG has also been effective in the treatment of intradermal local recurrences of breast carcinoma following a mastectomy.[19] It should be pointed out that this kind of local nonspecific immunotherapy has also been accomplished with the use of 2-4-dinitrochlorobenzene in the treatment of squamous and basal cell carcinomas of the skin.[20] After sensitization to this chemical, the patients' neoplasms are treated with topical applications of 2-4-dinitrochlorobenzene cream. More than 90 percent of superficial basal cell, or squamous cell, carcinomas have been destroyed by the local delayed cutaneous hypersensitivity reaction induced.[21]

Nonspecific immune stimulation with BCG has also been used as an adjuvant to chemotherapy in an attempt to induce a systemic effect. BCG vaccine was first used in this fashion by Mathe as an adjunct to chemotherapy for the treatment of leukemia.[22] Combining chemotherapy and immunotherapy increased the remission rate and prolonged the duration of response in these patients. Although two subsequent trials failed to confirm these observations, there were considerable differences in Mathe's trials and the subsequent two trials. Since that time a number of investigators evaluating a combination of chemotherapy and immunotherapy with BCG have indicated that administration of BCG alone, or in combination with allogeneic vaccine, is capable of increasing the duration of remission and the incidence of remission in patients with leukemia.[23]

BCG immunotherapy as an adjunct to surgical operation has been evaluated in several human neoplasms. However, the most extensive and thorough investigation of this surgical adjuvant modality has been evaluated in patients with malignant melanoma.[17,24] Following operation, patients with malignant melanoma, who have regional lymph node metastases, have a high incidence of recurrence, and it is felt that if immunotherapy is initiated immediately after surgical operation the microscopic residual disease can be more effectively controlled. A recent report by Eilber and co-workers has indicated that BCG immunotherapy used as an adjunct to surgical procedures in patients with malignant melanoma is capable of prolonging the disease-free interval in these patients.[24] In this study, excision of the primary malignant melanoma and regional lymph node dissection were done and patients were given BCG immunotherapy with or without allogeneic tumor cell vaccine. The interval from initial treatment to recurrence was plotted by the life table analysis method (Figure 1).

In patients treated with adjuvant immunotherapy there was a lower incidence of recurrence than in those treated by operation alone at all points on the graph. Immunotherapy also delayed recurrence (Figure 2). In 50 percent of the patients treated by operation alone, recurrence developed within four months. The median time to recurrence in the group treated by operation and immunotherapy was ten months. These findings suggest that BCG immunotherapy used as a surgical adjuvant when there is minimal residual disease is capable of increasing the disease-free interval.

BCG is currently undergoing extensive evaluation as a surgical adjuvant. One intriguing recent report by McKneally and associates describes the

use of intrapleural BCG administered as a surgical adjunct following pulmonary resection for lung cancer. The preliminary analysis of survival data indicates a definite beneficial effect of the intrapleural BCG.[25]

BCG comes in a variety of different preparations and strains. There is evidence that some strains are not as effective in immunostimulation as others. In addition, the dose of BCG seems to be important as well as the technique of preservation of the BCG organisms. All of these variables tend to explain some of the discrepancies in clinical trials when different strains of BCG are used in different doses and different techniques of preservation are used.

Both local and systemic complications of BCG immunotherapy have been described. The most severe toxicity of BCG occurs in patients who are receiving intralesional BCG, and who have extensive disease. Intratumor injection of BCG frequently results in fever, chills and localized abscesses with sinuses that drain for a relatively long time. Regional lymphadenitis is a frequent observation, and occasionally systemic infection has occurred associated with granulomatous hepatitis. Fatal anaphylactoid reactions have been described in patients receiving multiple injections of large doses of BCG intralesionally. Smaller doses of BCG should be used in patients with positive tuberculin tests. Pretreatment with antihistamines and aspirin before and several days after the intralesional injections decreases toxicity. Persistent symptoms have been treated successfully with isoniazid.

In contrast to intratumor injection with BCG vaccine, the administration of BCG by the intradermal multiple tine puncture technique is usually quite well tolerated with a low incidence of hepatic dysfunction, and only mild fever and malaise lasting for a short period of time following vaccination. Anaphylactoid reactions, or pronounced toxicity, has not been associated with this method of administration. The complications of BCG immunotherapy have been reviewed recently by Sparks.[26]

Some of the difficulties inherent in the use of live BCG organisms have stimulated interest in

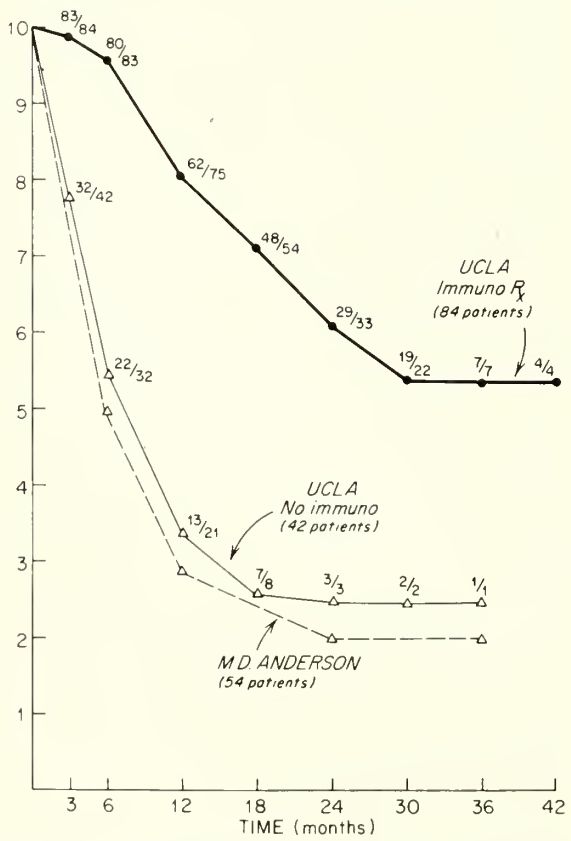

Figure 1.—Recurrence rate of Stage II melanoma, showing the percentage of patients free of recurrent melanoma after regional node dissection or node dissection with postoperative immunotherapy.

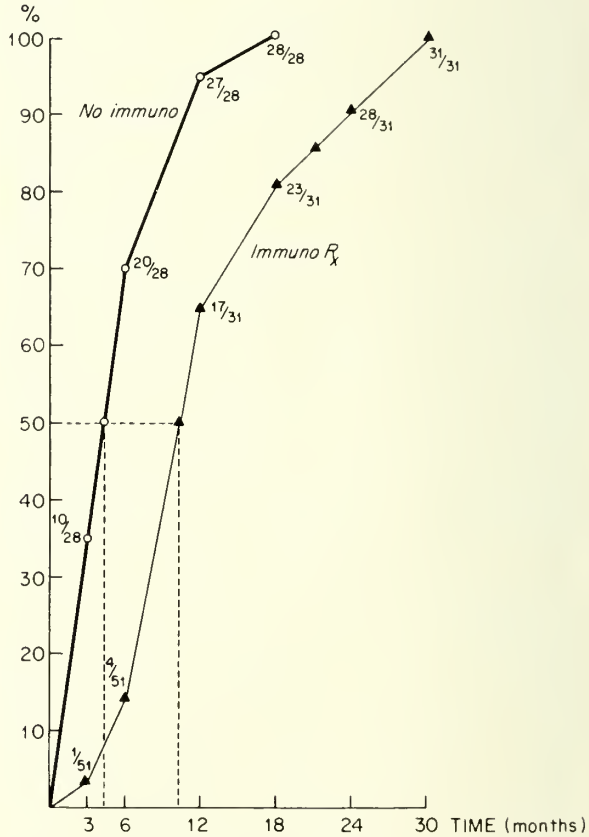

Figure 2.—Time to recurrence of melanoma after a disease free interval. Difference between disease free interval in those treated by surgical operation alone and those treated by operation and immunotherapy.

certain extracts of BCG. These extracts, such as methanol extractable residue (MER) and the Ribi vaccine, are currently being evaluated in clinical trials.[16]

Corynebacterium parvum

Corynebacterium parvum is a Gram-positive anaerobic organism. In contrast to BCG, C. parvum is not used as a viable organism, but is formalin killed. Also in contrast to BCG, it can be administered intravenously whereas BCG is not given by the intravenous route in man. C. parvum is a potent macrophage stimulator when given intravenously, and when given by this route it is a strong T cell suppressor.[27] However, when given by the intradermal or the tumor intralesional route, it is a T cell stimulator. This stresses, again, the importance of the route of injection in determining the mechanism of action of these immunostimulating agents.

C. parvum, like BCG, is very effective when given intralesionally, and it is also effective when mixed with tumor cells and injected into a region that is drained by the same lymph nodes that drain the tumor. It is effective as a surgical adjuvant in animals; however, the clinical experience with C. parvum as a surgical adjunct is not as extensive as with BCG and surgical adjunct trials in man are just beginning. While there has been relatively little clinical experience with the use of C. parvum as an adjunct to surgical operation or with its use as an intralesional agent, C. parvum has been evaluated extensively as an adjuvant to chemotherapy.

Israel and Halpern have reported on the use of C. parvum in combination with chemotherapy for a variety of solid tumors.[28,29] Patients who had the best prognosis were those who were immunocompetent before therapy, and who received C. parvum in addition to chemotherapy. The patients who received C. parvum in addition to chemotherapy had a longer duration of remission, a higher incidence of remission and maintained their immunological competence better than those patients who received chemotherapy alone. These trials were conducted in patients with disseminated carcinoma of the lung, advanced lymphosarcomas, breast carcinoma and advanced melanoma. The data indicated that the patients receiving C. parvum in addition to chemotherapy had a prolonged survival. Patients with good cell mediated immune function, as judged by reactivity to a variety of skin test antigens, responded better to C. parvum treatment than those with poor cell mediated immune function. Interestingly, the patients who received C. parvum had a better hemopoietic tolerance to the chemotherapy than patients not receiving C. parvum.

The initial Phase I trials indicated that C. parvum could have significant toxicity. Given by the subcutaneous route, pain, swelling, fever and chills frequently developed. Intravenously given C. parvum in doses in excess of 5 mg per sq meter has been associated with cyanosis, bronchospasm, and significant chills and fever. However, in doses between 2.5 and 3.5 mg per sq meter intravenously given C. parvum has been very well tolerated. The agent should be administered slowly intravenously for the first two to three injections. It is usually given weekly, and after three to four injections it generally can be injected more rapidly. The optimum dose and route of injection for induction of tumor immunity have not yet been defined.

The extensive experience with C. parvum and BCG in animal investigations and the clinical experience to date allow certain conclusions regarding the general principles of immunotherapy with these agents:

- It is clear that this form of immunotherapy is effective only against a limited amount of disease. Patients with large tumor burdens, in general, do not benefit from the administration of these immunotherapeutic agents alone. In view of the above, it is clear that immunotherapy should be used in combination with a major ablative modality such as chemotherapy, surgical operation or radiation therapy.
- Immunotherapy is most effective when the immunotherapeutic agent comes in close contact with the tumor. This may take the form of direct intralesional injection, or the injection of a nonspecific agent in combination with whole tumor cells or subcellular products.
- Immunotherapy generally does not induce regression of established tumors when given systemically.
- Experience has indicated that the immunotherapeutic agent should be administered, if possible, in the region which is drained by the same lymph node group that drains the neoplasm being treated.

Levamisole

Levamisole is an entirely different agent from C. parvum and BCG. Levamisole is a chemical

compound that can be taken orally in the form of a tablet. This agent was originally developed as an antihelmentic, and has been used extensively in Western Europe and other parts of the world to treat intestinal infestations in man. Its effect on the immune system was discovered by accident. There has been some reluctance to describe levamisole as a nonspecific immunostimulating agent because it appears to have little or minimal effect on an intact normal immune system. The most dramatic effects have been in patients with depressed immune function. When used as an immunotherapeutic agent in animal systems, levamisole has little effect on established animal tumors. In addition, it is not as effective as BCG or C. parvum as a prophylactic agent in animal tumor models. However, levamisole has been shown to effectively augment chemotherapy in animal neoplasms. It increases the duration of response, and the cure rate of chemotherapy, and also prevents the immunosuppression of chemotherapy in these animal models.[30-32]

The oral administration of levamisole has been shown to enhance phagocytosis and *in vitro* lymphocyte function in animals. In man, levamisole has been shown to have an effect on T cell function and macrophage function. It augments macrophage chemotaxis in man, and the elaboration of macrophage immobilization factor. In certain patients with depressed T cell levels, levamisole administration returns the T cells to normal levels. This has been observed in patients with Hodgkin's disease, systemic lupus, rheumatoid arthritis and herpes simplex.[33] In patients with the latter three diseases, the increase in T cell levels following the administration of levamisole is frequently associated with improvement in symptoms. The ability of levamisole to augment depressed delayed cutaneous hypersensitivity reactions in man is controversial; however, the weight of evidence suggests that it does.

This unique agent is currently undergoing extensive clinical trials. Two of these are of sufficient duration to merit discussion. Rojas has reported an impressive increase in the disease-free interval and survival in patients with locally unresectable breast cancer treated by radiation therapy and administration of levamisole.[34] In this study, patients with locally unresectable carcinoma, with no clinical evidence of distant metastases, were treated with radiation therapy with or without concomittant levamisole administration. After 30 months there was a statistically significant difference in the survival of patients receiving levamisole. Of the patients receiving levamisole, 90 percent were alive, whereas only 35 percent of the control group were alive. In addition, at 24 months the recurrence rate was statistically significantly different in favor of the levamisole treated group.

Levamisole has also been used as a surgical adjuvant following pulmonary resection for lung cancer.[35] In this study, which was done in Western Europe, patients undergoing pulmonary resection for lung cancer were treated either with placebo or levamisole. The placebo or levamisole was begun five days before surgical operation. Levamisole therapy was continued intermittently following operation until recurrence. Within certain disease categories there was an impressive difference between the patients treated with levamisole compared with controls. Small primary lesions with negative lymph nodes were not affected by the levamisole treatment. However, in those patients who had large primary lesions, vascular invasion or regional lymph node metastases, the survival of the patients receiving levamisole was significantly better than the control group. There was an interesting pattern of recurrences within the two groups. Patients receiving levamisole had a low incidence of distant recurrence, and when recurrence occurred it was usually local. Certainly these impressive clinical results in breast cancer and lung cancer require confirmation. There are trials currently underway in this country, and elsewhere, evaluating levamisole as an adjunct to surgical operation and other cancer cytoreductive therapy.

Levamisole, in the doses used in clinical trials, has had relatively few side effects. With 150 mg per day administered for three days every two weeks, the side effects have been quite acceptable. Occasionally patients complain of mild nausea, but this is relatively uncommon. No changes in hematological measurements have been reported. In higher doses levamisole has caused more consistent nausea, and occasional neurological symptoms such as hyperreactivity, increase in insomnia and agitation.[27]

Conclusions

A large number of data has been accumulated both in animal studies and in clinical studies indicating that the immune response is an important component of the host-tumor interaction. Several

clinical trials, although preliminary, indicate that immunotherapy may be a useful adjunct to the other forms of cancer therapy, such as radiation therapy, surgical operation and chemotherapy. However, it is becoming clear that immunotherapy, as it is currently used, has limited effectiveness. Immunotherapy alone is not effective against large amounts of tumor, and it is certainly most effective when all gross disease has been eliminated and only microscopic residual disease remains.

Our knowledge regarding the clinical application of immunotherapy is quite limited and many unknown factors remain to be defined. For example, the optimum dose of the immunopotentiators has not yet been defined, the duration of treatment necessary for maximum effect is unknown and much of the basic mechanisms of action has yet to be defined. For these reasons, and also because immunotherapy may actually accelerate tumor growth in certain conditions, the use of immunotherapy should be limited to those who are experienced in its use and who are conducting properly stratified, randomized trials in order to determine its most effective application in humans.

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Specialty Conference

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Taken from a Pulmonary Conference held at Stanford University.

Refer to: Liebhaber M, Robin ED, Lynne-Davies P, et al: Reye's syndrome complicated by Ondine's curse—Stanford University Pulmonary Conference (Specialty Conference). West J Med 126:110-118, Feb 1977

Reye's Syndrome Complicated by Ondine's Curse

MYRON LIEBHABER, MD: We are presenting a patient with hepatic failure and encephalopathy associated with loss of central nervous system (CNS) control of ventilation during sleep. The patient, a 4½-year-old boy, was well until seven days before admission. What appeared to be a varicella eruption developed, with a vesicular-papular rash beginning on the face and extending over the thorax. He was seen by a physician, given diphenhydramine hydrochloride (Benadryl®) for the itching and remained asymptomatic for two days. On the third day, after the eruption had crusted, a temperature of 105°F (40.6°C) developed, with vomiting and dehydration. The patient was admitted to Sacred Heart Hospital at Hanford, California, which is in the San Joaquin Valley. He was found to be lethargic with 10 percent dehydration. The laboratory workup showed normal cerebral spinal fluid values with a negative Gram stain, normal levels of protein and glucose. The only abnormal findings were a serum glutamic oxalic transaminase (SGOT) value that was not precisely quantified, but was greater than 2,000 IU, and a serum ammonia value of 280 μg per ml. Because of deterioration of neurologic status in the succeeding 24 hours, the patient was transferred to Kaweah Delta Hospital in Visalia, California. Upon arrival, he was found to be in stage 1 coma, responsive to deep pain, but no other positive physical findings. Initial laboratory studies disclosed the following values: leukocyte count, 20,000 with 41 percent polymorphonuclear leukocytes, 31 percent nonsegmented forms, 24 percent lymphocytes; SGOT, 10,040 IU, serum glutamic pyruvic transaminase (SGPT), 4,000 IU, serum ammonia, 200 μg per ml (normal, 80 μg per ml), and prothrombin time, 25 seconds (control, 12 seconds).

EUGENE D. ROBIN, MD: *Were electroencephalograms (EEG) made?*

DR. LIEBHABER: Yes, an EEG done during the first 24 hours showed diffuse slowing. On the second day he went from stage 1 coma to stage 4 coma; and after 24 hours, lost spontaneous respiration, with bradycardia down to 20 or 30 beats per minute. Intubation was carried out and the patient maintained on a ventilator. The first blood gas

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ABBREVIATONS USED IN TEXT
CNS = central nervous system
F_{IO_2} = inspired oxygen concentration
REM = rapid eye movement (sleep)
SGOT = serum glutamic oxalic transaminase
SGPT = serum glutamic pyruvic transaminase

studies on a ventilator at an inspired oxygen concentration (F_{IO_2}) of 70 percent showed an oxygen pressure (P_{O_2}) of 255 torr, a pH of 7.60, a carbon dioxide pressure (P_{CO_2}) of 27 torr and a bicarbonate value of 26 mEq per liter. On a radiograph of the chest normal lung fields with normal cardiothoracic ratio were seen. Twenty-four hours after intubation, decreased retinal venous pulsations and decorticate posturing were noted. Treatment was begun with intravenously given dexamethasone sodium phosphate (Decadron®) and mannitol injection (Mannitol®). During the subsequent five days, liver function returned to normal. He remained on the ventilator for the first week during which it was noted that he only occasionally triggered the ventilator. On the seventh day, a tracheostomy was done because of the apnea requiring dependence on the ventilator. Two days after tracheostomy, bilateral pulmonary infiltrates developed. Cultures taken through the tracheostomy grew Pseudomonas, sensitive to carbenicillin and gentamicin. Blood gas values deteriorated in that up to 80 percent F_{IO_2} was required, and carbon dioxide retention developed. Because of difficulty in managing the patient on the respirator at Kaweah Delta Hospital, he was transferred to Stanford on the tenth day for ventilatory support. During the first week at Stanford, his condition improved remarkably. The patient remained on the ventilator, but was brought down to room air. There were improved blood gas values, a return of P_{CO_2} to normal levels and clearing of pulmonary infiltrates.

DR. ROBIN: *When you say he improved remarkably, the two criteria of improvement were first the hepatic status and second the central nervous system status. Man does not live by breathing alone (although this is an important function). What happened to hepatic function and what happened to central nervous system function?*

DR. LIEBHABER: Hepatic function actually returned to normal by the fifth day. As for the CNS status, stage 4 coma was diagnosed because of absent respirations.

DR. ROBIN: *That requires a comment. If stage 4 coma is defined as loss of respiration, does not that depend on whether the patient is on a ventilator or not? Coma could be related simply to changes in blood gas values producing CNS depression. It also could be related to loss of central control of ventilation. Such patients can be entirely awake providing ventilation is maintained so that using the term stage 4 coma to denote loss of respiration does not really tell you what you want to know about central nervous system status. Independent of the patient's respiratory status—that is, whether he was able to breathe or not—what was his central nervous system status?*

DR. LIEBHABER: Initially he was arousable; however, he was quadraplegic. He was areflexic, he had an absent gag reflex, bilateral positive Babinski reflexes and ankle clonus.

DR. ROBIN: *He had persistent central nervous system disease which was really independent of the alteration of brain function by the apnea?*

DR. LIEBHABER: Yes. On the 45th hospital day it was decided to begin a ventilator weaning process. The patient was taken off the ventilator and remained on the tracheostomy tube for 15 minutes at a time. The total time off the ventilator was gradually increased. By the 60th day, he was off the ventilator and on a tracheostomy tube for five hours with normal blood gas values. He remained on the tracheostomy tube, awake and alert during the day. However, he refused to sleep at night unless the ventilator was turned on and, in fact, he lost spontaneous respirations while asleep. Neurologic status was improving, he was stronger, moving all four limbs and sitting up in bed watching television. However, sleeping respiratory rate remained 2 to 3 breaths per minute, while waking respiratory rate was 12 to 15 breaths per minute. On one occasion, during a daytime nap while off the respirator, he had a respiratory arrest with bradycardia down to 50 to 60 beats per minute. Because of his dependency on the ventilator at night, a 24-hour, continuous monitor sleep apnea study was done on the 88th day. It was noted that when he went to sleep (off the ventilator), there was an intrinsic respiratory rate of 1 to 2 breaths per minute. During the time off the ventilator, the arterial oxygen saturation fell to 40 percent and he became bradycrotic at 40 beats per minute. After a trial dose of 4 mg per kg of body weight of intravenously given aminophylline, the respiratory rate doubled from 1 to 2 breaths per minute to

4 to 5 breaths per minute. However, arterial oxygen saturation again fell to 40 percent and the patient became bradycrotic. A continuous EEG done during the study showed that when arterial oxygen saturation fell down to 40 percent, the EEG became hypersynchronous with high amplitude wave forms.

Between the 90th and 104th hospital day, there were four episodes of bradycardia and cyanosis. These episodes occurred during waking hours rather than while asleep. During this time, difficulty was encountered passing the suction catheter beyond the end of the tracheostomy tube. He also had difficulty in swallowing, with food flowing out of the tracheostomy after feeding. On cineesophograms esophageal dysmotility was noted, with contrast flowing freely down the trachea. An upper gastrointestinal series showed a hiatal hernia.

Because of the swallowing problem and the difficulty in maintaining him on the ventilator, he was taken to surgery on the 109th hospital day. On bronchoscopy a narrowing immediately distal to the tip of the tracheostomy tube was seen. (The narrowing appeared to be the result of granulation tissue secondary to chronic irritation at the tip of the endotracheal tube.) A tracheal dilation and strutting procedure were done along with a feeding gastrostomy and a hiatal hernia plication.

The patient's neurologic status continues to improve with increased strength and improved coordination. However, he continues to have an absent gag reflex, right facial paralysis, hyperactive reflexes and bilateral ankle clonus. Since he has been in the hospital, two EMI®* scans have been done that show a right frontal parietal lobe infarct. Apnea continues to be present and ventilatory support is required during sleep.

In summary, the patient is a 5-year-old child in whom, post-varicella, encephalopathy and hepatic failure developed compatible with Reye's syndrome. Subsequently the neurologic sequelae of a lack of spontaneous respiration during sleep developed with multiple cranial and peripheral nerve abnormalities.

Reye's syndrome is a fairly new entity, described 13 years ago as a syndrome of encephalopathy and fatty degeneration of the viscera. The pathogenesis is not understood, and current therapy is entirely empirical. In an epidemiologic study of Reye's syndrome done by the Center for Disease Control, criteria for defining the syndrome include: (1) Acute onset of encephalopathy; (2) Hepatic involvement, as evidenced by at least one serum SGOT or SGPT level of greater than 100 units (with little or no elevation of serum bilirubin) or evidence of massive fatty degeneration of the liver at biopsy or necropsy, or both, and (3) no other reasonable explanation of the cerebral and hepatic abnormalities.

The syndrome appears to be preceded by a clinical prodrome of 12 hours to four days. The prodrome consists of fever, vomiting, headache, diarrhea, lethargy, irritability and upper respiratory tract infection. The initial clinical presentation is usually abrupt, with convulsions, hyperventilation, fever and hepatomegaly followed by sustained coma.

PATRICIA LYNNE-DAVIES, MD:† *Am I right in thinking that the patient did not have convulsions when he was first seen?*

DR. LIEBHABER: No. After intubation was done and he was placed on the ventilator, he did have some posturing that was thought to be either seizures or increased intracranial pressure.

D. P. L. SACHS, MD:‡ *Is there any relationship between the high fever and the development of the encephalopathy?*

DR. LIEBHABER: This child did have a high temperature of 105°F, but in Reye's syndrome the fever can be quite variable.

The initial laboratory findings include hypoglycemia, a prolonged prothrombin time, elevated SGOT and SGPT levels and hyperammonemia. The most consistent acid-base disturbance in children with Reye's syndrome appears to be metabolic acidosis. Histopathology of liver biopsy tissue obtained early in the evolution of Reye's syndrome shows mitochondrial swelling and "small-droplet" triglyceride accumulation. During clinical recovery, mitochondrial morphology improves. The agents that have been implicated with either epidemic or single cases of Reye's syndrome include toxic agents such as salicylates, bush tea alkaloids causing the vomiting sickness of Jamaica, aflatoxin produced by aspergillus flavus, and various viruses such as influenza B

*This is a specific brand name for the technique of computerized axial tomography (CAT scanning) manufactured by Electronics Musical Industries, Inc. The unusual name derives from the fact that the method was developed at a company originally involved in manufacturing electronic musical instruments.

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and varicella (as seen in our patient). As far as the pathophysiology, various enzyme deficits have been implicated in the mitochondrial portion of the ornithine-citrulline cycle, such as ornithine transcarbamylase and carbamyl phosphate synthetase.

FRANK SINATRA, MD:* The recent interest in the hepatic mitochondrial enzymes of the urea cycle as they relate to the pathogenesis of Reye's syndrome was largely generated by the observation a few years ago that in patients with Reye's syndrome there are some striking clinical and laboratory similarities to patients with congenital disorders of urea biosynthesis. During the acute phase, both groups of patients are characterized by vomiting, irritability, hepatomegaly and progressively severe encephalopathy. Laboratory evaluation shows elevated blood ammonia and transaminases as well as depression of liver-dependent coagulation factors. Despite the often severe hepatic dysfunction, the bilirubin value is normal or only minimally elevated. In addition, studies of serum amino acids in patients with Reye's syndrome show patterns very similar to those seen in congenital carbamyl phosphate synthetase (CPS-I) and ornithine transcarbamylase (OTC) deficiency. These two enzymes make up the mitochondrial portion of the urea cycle and are necessary for the conversion of ammonia to carbamyl phosphate and for its subsequent conversion to citrulline. A defect in one or both of these enzymes appeared an attractive way to explain many of the pathophysiologic events in Reye's syndrome, especially in view of the ultrastructural changes noted in hepatocyte mitochondria by Partin and co-workers.

Over the last two years our group, as well as others, has shown pronounced reductions in the activity of these two enzymes in the liver during the acute phase of Reye's syndrome. Our studies suggest that these defects may be most prominent during the first 72 hours following the onset of encephalopathy and may rapidly return to normal later in the illness, despite the fact that a progressive downhill encephalopathy may continue. This time course is similar to that observed for the laboratory evidence of hepatic dysfunction and the hepatocyte mitochondrial ultra-structural changes.

The biologic significance of these *in vitro* observations and the relative importance of ammonia intoxication in the production of the encephalopathy are unknown. We have no evidence at present to suggest that these defects are genetic in origin in most cases. Our current impression is that they represent an acquired and reversible process related to the more primary problem of mitochondrial injury.

DR. ROBIN: I think a comment is appropriate. These are very interesting observations, but they do pose a problem pathogenetically. The problem is whether the encephalopathy is really connected with the injuries to the liver or whether it is not. The reasons for this question are two-fold: One is that at least in most described forms of liver injuries, this type of encephalopathy is unknown; an encephalopathy associated with prolonged coma, with paralysis and brain stem manifestations for long periods. I do not think it is easy to attribute the encephalopathy to the liver disease. Second, it is difficult to assume that the hepatic enzyme abnormalities play a role in the generalized disease. Brain mitochondria do not contain urea cycle enzymes, or at least these have not been described in brain tissue. Therefore, the encephalopathy cannot be easily related to liver disease. If there can be no direct alteration of urea cycle enzymes in the brain, since brain mitochondria lack these enzymes, then it does cast some doubt as to whether the enzyme abnormalities constitute the generalized biochemical lesion. If ultimately a single biochemical lesion is found that accounts for all of the abnormalities, it is doubtful that ornithine transcarbamylase or carbyl phosphate synthetase alterations will prove to be the specific biochemical lesion.

JAMES THEODORE, MD:† *You are talking specifically about Reye's syndrome?*

DR. ROBIN: Yes.

DR. SINATRA: I think Dr. Robin's point is a very important one and one I should have emphasized. Although the hyperammonemia associated with hepatic failure probably contributes to the encephalopathy, I strongly doubt that hepatic encephalopathy is the only or even the primary mechanism involved. Certainly the studies by Dr. Partin's group showing there to be mitochondrial changes in the brain similar to those observed in hepatocyte mitochondria would support the view that the brain may be a primary rather than secondary site of involvement.

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DR. THEODORE: *Dr. Sinatra, from what you have said the changes found in hepatic encephalopathy, in general, are found with acute liver decompensation, arising from a variety of causes. Many of the substances you have associated with Reye's syndrome are also found in other patients with prehepatic coma in whom hyperventilation and the other manifestations are present. Do you think this model might be an expression of what's involved in terms of hepatic encephalopathy in general rather than the specifics we are talking about today?*

DR. SINATRA: I think the control of hyperammonemia in these children may very well be beneficial, but I doubt that this is the entire explanation for the encephalopathy.

DR. ROBIN: In most forms of hepatic encephalopathy if you reverse the underlying liver disease you will reverse the encephalopathy, but that is not the case in Reye's syndrome. I also think (and I guess that Dr. Lewiston would agree) that it is very dangerous to draw conclusions from abnormal mitochondrial ultrastructure. We think that simple mitochondrial edema can produce very profound changes in both structure and function of mitochondria independent of the mechanism that's producing it.

DR. LIEBHABER: The resolution of the hepatic function seems to have no prognostic significance.

DR. THEODORE: *Dr. Robin, at this point, why don't you give us some background on Ondine's curse and some of the other ventilatory abnormalities associated with central nervous system disorders?*

DR. ROBIN: This is the first reported case of Reye's syndrome associated with what seems to be largely irreversible changes in the automatic control of breathing. In that context, it might be interesting to point out that in the last five or six years it has become possible to develop a general approach to disorders affecting the central control of ventilation. One can begin to make sense out of what seemed to be a widely separate group of disorders including Ondine's curse, the pickwickian syndrome, central primary hypoventilation and sleep apnea. The basis of this general approach is shown in Table 1.

The central control of breathing has two important components which can operate independently but also are interrelated. One component involves the voluntary maintenance of ventilation through contributions of the central nervous system. Knowledge of these disorders provides two kinds of information; one kind of information provided assists the localization of the neurological abnormalities. It also not uncommonly provides some kind of clue as to what might be taking place in a pathogenetic fashion. In epileptic seizures that involve structures of the limbus there is so-called epileptic apnea, a complete cessation of breathing, usually for relatively short periods. In central hemiplegia of the usual kind, say with unilateral lesions involving the capsule, there is decreased voluntary ventilation that is unilateral. This finding may assist the diagnosis of cerebral vascular thrombosis. The patient may have perfectly normal regular breathing. If you ask the patient to take a voluntary breath, that is remove automatic control of ventilation, there will be an inhibition of thoracic movement on the contralateral side of the central lesion. So just as you might test for a unilateral Babinski sign or the presence of aphasia, a voluntary breath may be used to locate the neurologic lesion.

With pseudobulbar palsy, when patients are asked to take voluntary breaths, you may find that they are unable to do so in a coordinated fashion. Although these patients have completely normal automatic breathing, during voluntary efforts, breathing becomes uncoordinated. The lesions in pseudobulbar palsy are usually fairly diffuse, but are above the brain stem. With extrapyramidal disease, patients may show "respiratory apraxia." That is, again, when you ask a patient to take voluntary breaths, the breathing pattern becomes quite uncoordinated. The difference between the pattern with pseudobulbar palsy is that the patient will also have uncoordinated swallowing and

TABLE 1.—*Disorders Associated with Abnormal Central Control of Ventilation*

- Abnormalities of Voluntary Control
  - Epileptic apnea
  - Central hemiplegia
  - Pseudobulbar palsy
  - Respiratory apraxia
  - Bilateral pyramidal destruction
- Abnormalities of Automatic Control
  - Apneustic breathing
  - Central alveolar hyperventilation
  - Central alveolar hypoventilation
    - Direct lesions of carbon dioxide receptors
    - Lesions of medullary respiratory neurons
    - Lesions of descending medullary axons supplying respiratory muscles

emotional manifestations. With pure extrapyramidal involvement, the only effect seems to be on the voluntary control of breathing. Patients have been described with bilateral destruction of the pyramids who have survived for several days and have shown a complete inability to take voluntary breaths although automatic control is well maintained. If these patients are tested by exposure to high concentrations of carbon dioxide, they show an increased sensitivity to carbon dioxide, indicating that the automatic control of ventilation is not only intact but may actually function in a supranormal fashion once complete voluntary paralysis occurs.

The automatic control of breathing is also associated with more or less specific neurological syndromes manifesting themselves in abnormalities of ventilation. Lesions which involve the tegmentum of the pons may be associated with the development of apneustic breathing, that is, breathing in which there is maintained inspiration for long periods of time. There is at least one patient with such a lesion who survived for 48 hours in which all of the gas exchange was basically carried on while the patient was apneustic. All of you, I am sure, have seen patients who present with central nervous system disease, without fever and without overt metabolic abnormalities, in whom there are high minute volumes of ventilation and intense alveolar hyperventilation. In general, this manifestation is associated with midbrain lesions.

In the medulla, there appear to be at least three kinds of lesions capable of producing substantial decreases in the automatic control of breathing. One of these is a direct lesion of the carbon dioxide receptors inside of the medulla, the second are abnormalities which involve the medullary neurons and the third are lesions involving the descending axons from the medullary centers going directly to the respiratory muscles. In the face of quadraplegia, this could be the lesion in our patient. With this background, let us discuss Ondine's curse. First of all, it should be pointed out that in diseases of automatic control there appears to be a spectrum of involvement. There are patients who have such severe lesions that automatic control of breathing is lost both during waking and sleep; such patients require ventilatory support indefinitely or die of the underlying disease. At the other end of the spectrum are patients who have alterations of automatic control that are more modest. The patient in the steady state has alveolar hypoventilation with a low P_{O_2} and a high P_{CO_2}, but is able to get along even during sleep with a lesion not severe enough to produce life-threatening or life-taking apnea. There also are patients in between these two extremes.

Incidentally, one important characteristic of damaged automatic control is that when patients are asked to evoke voluntary control of ventilation their blood gas values completely return to normal. This provides an interesting contrast. Patients with abnormal voluntary control may have normal (or supranormal) automatic control. The abnormality in abnormal central regulation may only become obvious when the patient is asked to ventilate voluntarily. Patients with abnormal automatic control may have normal voluntary control. The abnormality in central regulation may only become obvious when voluntary control is eliminated. The loss of ventilation with sleep in our patient justifies the designation of Ondine's curse.

That brings up a critically important scientific question (recently raised by Dr. Julius Comroe, Jr.*) as to whether the term "Ondine's curse" is ever appropriate. Dr. Comroe undoubtedly has the finest mind among pulmonary physiologists of the past 30 years and is one of my heroes. However, his rejection of Ondine's curse might be questioned. The literary basis of his rejection is that no Ondine ever cursed her unfaithful swain. Since the term "Ondine" dates from the time of Paracelsus (1500's), there are a number of versions of the myth. Drs. Severinghaus and Mitchell (who coined the term) are entitled to their version as is Dr. Comroe entitled to his version. Ondine's curse represents the curse associated with being unfaithful to Ondine and did not necessarily originate from her. Even if she cursed Hans (Ondine's lover), would she have admitted it openly? After all, Hans did die in an unusual way, so that *clearly* some kind of curse must have been operating. The scientific basis of his rejection is that the term "Ondine's curse" (according to Dr. Comroe) was meant to describe a specific type of respiratory failure. I think that this interpretation is open to question. Since the regulation of breathing involves numerous segments of the CNS, it could well be associated with a number of lesions rather than a single lesion. Although it is difficult to pinpoint Hans's neuro-

*Dr. Comroe is Morris Herzstein Professor of Biology and Professor of Physiology at University of California, San Francisco.

logic lesions (loss of blue-green color vision, loss of focal skeletal muscle activity, loss of hearing, loss of smell, loss of touch with retained speech) specifically, the widespread distribution of lesions does not rule out "Ondine's curse" as the cause of his death. The elements making up a diagnosis of Ondine's curse include (1) essentially normal lungs and chest wall as shown by (2) the ability to normalize Po_2 by voluntary effort (indicating normal oxygen exchange within the lung) and (3) no florid respiratory failure with active voluntary control (the waking state) but the precipitation of severe alveolar hypoventilation with diminished voluntary control (sleep). Our patient, certainly, and Hans, less certainly (no blood gases or pulmonary function data are available), meet these criteria.

In addition to Ondine's curse, there are a number of other terms used to describe disorders of automatic control. Primary central hypoventilation is one such term used to describe patients commonly showing alveolar hypoventilation during the waking state. In recent years, the term sleep apnea has been emphasized. Patients with sleep apnea may be classified into three groups. One is the so-called mechanical group, the second is the central group and the third is the combined group. The mechanical group may be separated into two types. There are patients in whom mechanical obstruction develops during sleep, probably related to relatively well-defined diseases. For example, alveolar hypoventilation related to exuberant tonsils and adenoids in children may become worse during sleep. Other patients apparently have a pathological relaxation of the posterior pharynx during the sleeping state and consequently during sleep severe respiratory obstruction leading to alveolar hypoventilation develops. Even in this group it appears that medullary centers (involving cranial nerves IX and X) are involved in the abnormal relaxation of the pharyngeal muscles that produces high airway obstruction. Therefore, there appears to be an important neurogenic central component in mechanical sleep apnea.

The second group of patients (there is a case report in a recent issue of *Annals of Internal Medicine* describing this group) is made up of patients who have sleep apnea related to abnormal automatic control without mechanical factors, and our patient today, of course, is an example of this form of sleep apnea. We suggest that this group is the same as patients with Ondine's curse. Finally, there are patients with combined mechanical and neurologic factors. Ara Tilkian (formerly a fellow in the Cardiology Division) has made important contributions in this field. He has shown that during sleep apnea, severe cardiac arrhythmias may occur, posing an additional threat to life.

Another disease that is part of this group of disorders is the pickwickian syndrome. Pickwickians are patients who, while obese, develop severe alveolar hypoventilation. In a pure pickwickian, the alveolar hypoventilation largely disappears with the loss of weight. It is probable that all pickwickians have some depression of the automatic control of breathing. Obesity imposes an additional mechanical problem as well as causing abnormal pulmonary gas exchange. Without obesity, they would probably not show alveolar hypoventilation, but the combination of the mechanical and gas exchange abnormalities resulting from obesity plus their altered medullary state precipitates alveolar hypoventilation. By ameliorating the mechanical abnormalities by weight loss, alveolar hypoventilation can be reversed.

An interesting relationship between pulmonary mechanics, the control of ventilation and sleep, has been described by Charles Bryant at the Hospital for Sick Children in Toronto. Dr. Bryant and his colleagues are exploring an approach to the measurement of respiratory center sensitivity which was developed by the Montreal group. (Dr. Lynne-Davies knows more about this than I.) The approach is as follows: An attempt is made to estimate central respiratory drive while carrying out tidal volume studies by occlusion of the mouth and measurement of peak inspiratory pressure during the first 100 milliseconds (P_{100}). The theory is that this provides some index of respiratory drive independent of mechanical factors. Dr. Bryant studied neonates and he found that during the waking state the youngsters generated reproducible curves. When he studied them during sleep he found that the curves tailed off. Most people would have ignored this disparity. He, however, did not and he found that the decrease in P_{100} only took place during rapid eye movement (REM) sleep. During REM sleep, there was a depression of P_{100}.

LAWRENCE M. SIMON, MD:* *Why does that pressure necessarily reflect the central drive? If one*

*Assistant Professor of Medicine.

had weak muscles, would not there also be depressed pressure?

DR. ROBIN: That is correct; however, it is felt that by using each curve as its own control, you can at least use it for pertubations and factor out nondrive factors such as muscular weakness.

DR. SIMON: *So that one curve would be the maximal that the whole central and neuromuscular apparatus could produce?*

DR. LYNNE-DAVIES: I think the argument as to why it would reflect central activity is that in an animal preparation, an enormous variation in tidal volume can be produced by a combination of rebreathing (or carbon dioxide breathing) and applying elastic loads which minimize tidal volume. Regardless of the mechanical or chemical drive applied, when tidal volume is plotted against the duration of inspiration, all breaths fall on the same level before vagotomy, while the time intercept at zero volume is roughly the same before and after vagotomy. This implies that you can distinguish what is going on in the lungs from what is going on with vagal feedback versus centrally. So, it is not only the volume-pressure relationship that is important, but also the volume-time relationship.

DR. ROBIN: Indeed, what Dr. Bryant found was a mechanical change during REM sleep. By placing magnetometers appropriately, he could measure the volume of ventilation produced by the rib cage which he felt was largely intercostal and the volume of breathing produced by diaphragmatic activity. During quiet sleep or presleep or during the waking state, both the diaphragm and the intercostal muscles are in phase, and of course that is an ideal mechanical circumstance because both groups of muscles are additively producing an effective tidal volume. During REM sleep, the intercostals and diaphragm function out of phase and while the diaphragm is zigging the intercostals are zagging. What REM sleep seems to cause is asynchronous neural input. The basis of the phase lag is a local reflex which he calls the "phrenic inspiratory inhibitory reflex." With additional added mechanical work, the asynchrony could be accentuated. With pickwickians, or with other patients with abnormal automatic control, the superimposition of mechanical abnormalities on the neurologic abnormality might be synergistic and could account for more distortions in both mechanics and gas exchange than could be accounted for by either lesion alone. As a first approximation, this may account for the pickwickian syndrome. The abnormalities found in the neonate, and indeed the abnormalities present in many patients who have sleep apnea, represent some degree of abnormality of the mechanical properties of the lungs and chest superimposed on a basic neurogenic lesion. It should also be pointed out that long-term neurologic abnormalities are rather unusual in Reye's syndrome. The mitochondrial lesions in both liver and brain appear to be potentially reversible. The usual conception of the disorder is that patients either recover completely or die. To some extent, the persistent neurologic abnormalities (including defective automatic control) are atypical.

The final comments concern management. I believe that there is essentially no chance that either of the chemical agents proposed for improving respiratory center response in our patient (progesterone or chlormipramine) will help. On the other hand, these should be tried since they pose no major risk. If it turns out, as I suspect, that these agents are ineffective, then I think one or two things can be done. One would be to implant suitable electrodes to trigger the diaphragm. I think that there are sufficient data which suggest that electrodes are useful in the group of patients who need limited diaphragmatic pacing, say during sleep. The other possibility is to consider some form of assisted ventilation such as a rocking bed during sleep. I have not seen this child, but if it turns out that his pulmonary and chest wall mechanics are largely normal, a rocking bed or cuirase ventilator could be adequate. There is a reasonable possibility that he could be provided with a relatively high quality of life for an indefinite period of time and that possibility should be offered. I would stay away from use of an iron lung. It is psychologically difficult because of the patient's confinement.

DAVID LAMAN, MD:* *Where does posthyperventilation apnea fit into your organization?*

DR. ROBIN: That apparently is a sign of diffuse frontal lobe disease. This is the basis of the Plum test. The patient hyperventilates, and the length of apnea induced in the posthyperventilation period is noted. In a normal person, it is almost impossible to produce apnea by even severe hyperventilation. In patients with cortical disease, apnea will occur.

*Fellow in Respiratory Medicine.

JUDITH PICKERSGILL, MD:* *In the past, you have discussed the "backup control" of respiration involving gasping. Why has it been lost when it is most needed here?*

DR. ROBIN: I don't know. I have not discussed the peripheral control of ventilation or the "gasp" response. In the *Journal of Clinical Investigation,* several months ago, there's an interesting paper by Warren Guntherow which suggests that terminal gasping is related to a central nervous system set of controls that does not involve any of the usual automatic or voluntary pathways nor does it involve the peripheral chemoreceptors. The gasp is a primitive response, is resistant to tremendous degrees of hypoxia and may represent then the last regulatory mechanism that maintains life when all other ventilatory control mechanisms are lost.

DR. LIEBHABER: *I wonder if the child may have a component of both automatic and voluntary loss of control although he is still hypoventilating. Even while awake, he breathes only 12 to 15 breaths per minute.*

DR. ROBIN: The way to test his voluntary system is to have him voluntarily hyperventilate. If he could bring down the P_{CO_2} to 35 torr, this would indicate that his voluntary control is probably intact.

DR. LYNNE-DAVIES: *This brings up the question I have been wondering about: whether this case is an example of central hypoventilation. The evidence for that seems to be rather marginal in somebody who at one stage was quadraplegic and still apparently is at least quadraparetic. The patient had very pronounced muscle weakness at one time and there is no guarantee that all muscles are going to recover at the same rate.*

DR. ROBIN: Lesions have been described, for example, with lateral cordotomy, severing the outflow coming from the medulla and giving rise to Ondine's curse without muscular weakness. So, the fact that he did have quadraplegia does not mean that he has muscular involvement. Indeed, I think the fact that sleep so strikingly precipitates apnea strongly argues against peripheral muscular involvement as a major mechanism.

DR. LYNNE-DAVIES: I would certainly argue in favor of the central one, but it would not by any means, it seems to me, exclude the possibility that when he is asleep there is a combination of two factors. One is weakness plus loss of the voluntary component and this then precipitates complete apnea.

DR. ROBIN: I think one would be able to show that his respiratory muscle performance, at least for individual acts like flow rate, vital capacity, and maximum voluntary ventilation (MVV), will be largely intact. I am not certain that that is the case, but that would be my guess.

DR. LYNNE-DAVIES: I think that there is something missing at present. We do not have any of these more objective measurements to look at.

DR. ROBIN: I think that your point is well taken. I really should have mentioned that when tracheal stenosis developed, I feel that both a central lesion and a mechanical lesion were present and this therefore illustrated the point of the synergistic effect of both mechanical and neurogenic abnormalities. I also should have mentioned that the limiting fact to long-term survival may turn out not to be alveolar hypoventilation because that can be controlled, but may be a development of recurrent pulmonary infections and destruction of lung tissue due to aspiration and inability to handle pulmonary secretions.

In summary, this patient appears to provide the first example of impaired automatic ventilatory control associated with the encephalopathy of Reye's syndrome. During the waking state, automatic control is sufficiently intact so that gas exchange is reasonably normal. During sleep, respiratory failure with apnea supervenes. This justifies the title of Ondine's curse. The major therapeutic proposal involves the possibility of ventilatory support during sleep. Above all, this case illustrates striking advances in our knowledge of the neurophysiological basis of ventilatory control.

*Fellow in Respiratory Medicine.

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Refer to: Current diagnostic uses of computerized tomography in clinical medicine—Medical Staff Conference, University of California, San Francisco. West J Med 126:119-126, Feb 1977

Current Diagnostic Uses of Computerized Tomography in Clinical Medicine

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Associate Professor of Medicine, and H. David Watts, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, CA 94143.

DR. SMITH:* *There has been a remarkable increase in the use of advanced technology in medical practice during the past decade. This adds to the complexity and expense of diagnosis and therapy, but also lends new assistance to physicians. Perhaps the area where the advances have been most impressive in recent years lies in the use of computerized tomography to image previously inaccessible organs noninvasively. We are pleased to have Dr. Melvyn Korobkin with us today to review the current status of this technology and its application to the diagnosis of diseases of abdominal organs.*

DR. KOROBKIN:† There are few advances in medicine that can be considered revolutionary, but computerized tomography truly represents such a phenomenon. Many by now are familiar with computed tomography (CT) of the brain, a noninvasive way of imaging known or suspected lesions, whether they be tumors, infarcts, hematomas or abscesses. In the four short years since this technique was introduced into clinical practice, CT brain scanning has met almost unanimous and enthusiastic approval by neurologists, neurosurgeons, radiologists and patients. The presence of brain computerized tomographic scanners in this country has spread rapidly. There is convincing evidence that the number of pneumoencephalograms carried out has dropped drastically, with a similar but lesser decrease in the number of cerebral arteriograms.[1] The recent controversy[2] regarding the high cost of CT scanners and their relationship to regional health care planning should not obscure the unparalleled advantages of CT scanning for a patient in whom a structural brain lesion is suspected.

During the past year prototype models of a CT scanner capable of performing a scan in less than 20 seconds have produced cross section images of the body of remarkable clarity and diagnostic utility. The radiology department in this medical center acquired one of the first of these prototype models, and it is the purpose of my presentation today to show several examples of CT body scanning images, to describe some of the salient clinical and anatomic features of these images, and to speculate where I think CT scanning will be most useful in clinical practice.

CT scanning differs from conventional radiology

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†Melvyn T. Korobkin, MD, Associate Professor in Radiology.

ABBREVIATIONS USED IN TEXT

CT = computed tomography
SMA = superior mesenteric artery
VMA = vanillylmandelic acid

in several ways. Although x-rays pass through the patient during a CT scan, the detector in the system is a scintillation phototube or a gas-filled ionization chamber, rather than the usual x-ray film. The x-ray tube and the detector system are on opposite sides of the patient, and during an individual scan they rotate about the patient recording information about the internal structure of the thin transverse cross section through which the x-ray beam is passing. The data obtained by the detectors are processed by a high speed minicomputer. Through a complex series of mathematical manipulations the computer "reconstructs" the cross sectional image as an array or grid of picture elements and displays it as an integrated picture on a television monitor. The image seen on the television screen actually represents an analogue display of the digital solutions of thousands of simultaneous linear equations, with each numerical value on the grid representing a close approximation to the x-ray attenuation coefficient of the corresponding tissue within the patient's body. In most cases, the x-ray attenuation coefficient can be conveniently considered to represent the physical density of the tissue. The image on the screen bears a remarkable resemblance to photographs from standard atlases of cross-sectional anatomy. It must be remembered that these images are obtained with the patient lying comfortably on a table, and with the exception of occasional injection of intravenous contrast material, the procedure is free of any pain or significant risk or danger.

Table 1 lists the advantages and disadvantages of CT body scanning compared with conventional radiographic procedures. A CT scan is a cross-sectional tomogram, displaying an image of a plane approximately one centimeter in thickness. The transaxial orientation of the tomogram is at right angles to the orientation of conventional radiographic tomography, permitting visualization of normal and abnormal tissue in the dorsal-ventral direction. The most important feature of computed tomography is its ability to differentiate tissues of very similar density (or more precisely, of similar ability to attenuate an x-ray beam).

One can see different tissue elements on a conventional radiograph only when their densities differ by at least 5 percent. This permits delineation of tissues consisting largely of water, fat, bone or calcium from one another, but abnormalities within the major visceral organs or soft tissues themselves are rarely appreciated without the introduction of contrast media. The density resolution of computed tomography is of the order of one percent. This resolution provides images of tissue contours and internal organ structure previously unavailable in clinical medicine.

The disadvantages of CT body scanning are mostly its cost and the length of time required to carry out an examination. At present a CT scanner costs approximately $500,000. Most scanners require three or four minutes for the computer to process the data and reconstruct each image, resulting in a total examination time of at least one hour for a typical patient requiring 8 to 12 images. The cost to the patient, therefore, is higher than for most radiologic procedures (except angiography). The radiation dose to the patient is approximately that received during a barium examination of the gastrointestinal tract. Although the radiation dose is much less than for an abdominal angiogram, the usual precautions regarding unnecessary radiation must be exercised—especially in children and young women.

Table 2 lists the three general uses of CT in this hospital and the few other institutions where it is available. CT is a noninvasive way of confirming or excluding the presence of a structural lesion, usually a mass lesion, within the tissues or organs

TABLE 1.—*Advantages and Disadvantages of Computed Tomography Body Scanning*

Advantages
Tomographic focusing
Transaxial view
Remarkable density resolution
Minimal discomfort or danger
Disadvantages
Cost
Length of procedure
Moderate radiation dose

TABLE 2.—*Uses of Computed Tomographic Body Scanning*

Determine the presence or absence of a structural lesion.
Determine the size and extent of the lesion.
Suggest the specific diagnosis of the lesion.
Monitor the effect of therapy on the size and extent of the lesion.

of the abdomen. In addition to detecting the presence of an abnormality, certain lesions have a characteristic CT density that permits a specific pathologic diagnosis to be made. Even when a diagnosis is made or can be made by other modalities, CT body scanning permits a convenient and unique way to plan appropriate therapy—especially if radiation therapy is indicated—and to follow the effect of specific therapy on the extent of the lesion.

As I just indicated, most of the early experience with CT body scanning has centered on studies of the abdomen. It has been especially useful in studying the pancreas and retroperitoneum where conventional imaging procedures, including diagnostic ultrasound, have major limitations. Although there are certain anatomic sites outside the abdomen where the use of CT may be valuable, especially the pleura, mediastinum, and soft tissues of the extremities and axial skeleton, I will confine my discussion today to computed tomography of the abdomen.

General Studies of the Abdomen

Cross sectional images of the abdomen vary in their quality and utility in proportion to the amount of retroperitoneal and perivisceral fat present. This fatty material, producing a low density background to the reconstructed images transmitted to the television monitor, is responsible for the clarity and definition of the borders of the individual tissues and organs. Although some of these organs differ from each other in CT attenuation numbers (and therefore different shades of gray on the television screen), the perivisceral fat exerts the major influence on the useful visualization of abdominal structures (Figure 1). Obese patients generally have a large amount of abdominal perivisceral fat, but a surprising number of nonobese patients may also harbor this radiologically useful characteristic of body constitution. Obviously emaciated patients usually have very little perivisceral fat, often leading to a nondiagnostic examination[3] (Figure 2).

Intraperitoneal fluid or ascites can be easily identified by a separation of the liver and spleen from the adjacent rib cage by tissue with the approximate density of water, a density lower than that of the parenchymal organs. If this separation is limited to the liver or spleen alone, hemorrhage

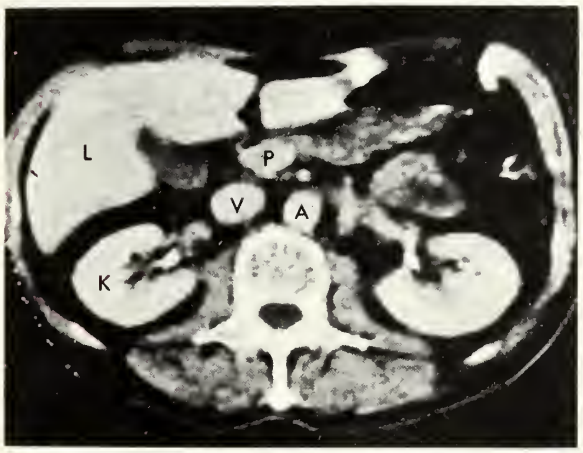

Figure 1.—The view is looking up from the supine patient's feet. A generous amount of abdominal fat helps outline the liver (L), kidneys (K), aorta (A), inferior vena cava (V), left renal vein (RV), and body and head of the pancreas (P). Notice the superior mesenteric artery between the aorta and pancreas.

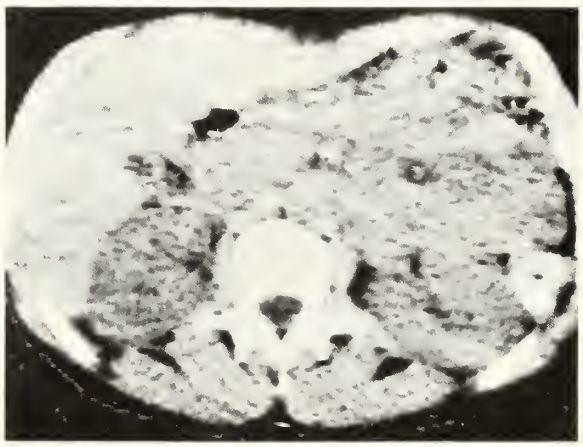

Figure 2.—Virtual absence of perivisceral fat in this patient makes it difficult to delineate the abdominal organs.

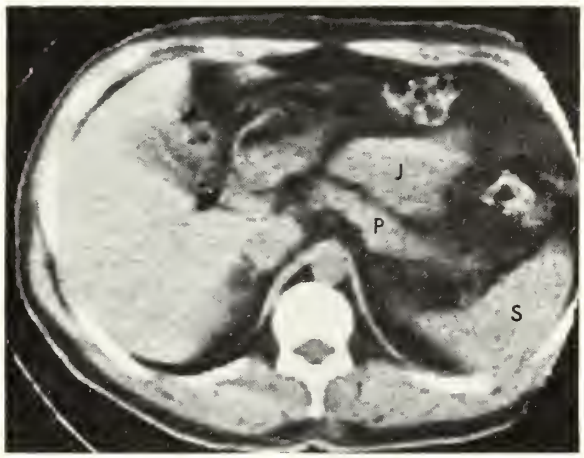

Figure 3.—The tail and body of the pancreas (P) appear normal in size, shape and texture. Also seen in cross-section are the liver, spleen (S), jejunum (J) and colon.

from that specific organ should be considered. Diffuse or localized high density medium within the lower density intraperitoneal fluid has been observed in patients seeded with metastases[3] or with presumed clotted blood following a biopsy study of the liver.

Pancreas

There has been widespread enthusiasm surrounding the use of CT in the evaluation of known or suspected pancreatic disease. Both the normal and abnormal pancreas can be routinely imaged in most patients. Only when there is a pronounced paucity of perivisceral fat in the abdomen is it difficult to visualize the size and contour of the pancreas.

Certain anatomic features help define the normal organ. Although the pancreas may occasionally lie horizontally in the abdomen and be seen on a single transverse section, most often it assumes an oblique orientation, only specific portions appearing on two or three successive levels. The tail usually appears on the highest section, adjacent to the splenic hilum and the upper pole of the left kidney (Figure 3). The body is identified as the curving structure just anterior (ventral) to the superior mesenteric artery (SMA) and its surrounding plane of fat. This particular relationship to the SMA is important because the third

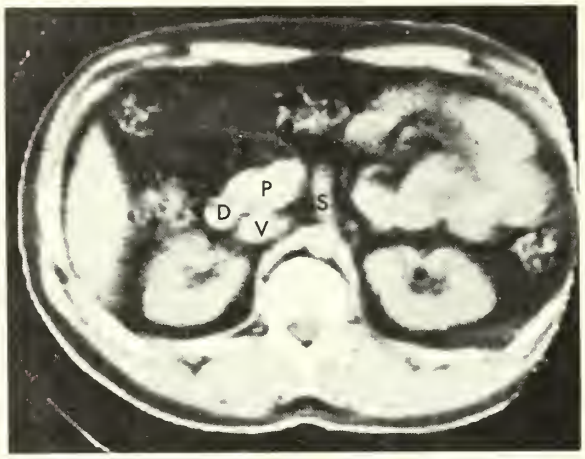

Figure 4.—A normal head of the pancreas (P) is seen between the duodenum (D), inferior vena cava (V) and superior mesenteric artery (S).

Figure 6.—A pseudocyst in the head of the pancreas (Ps) is seen as a well-circumscribed, low density mass.

Figure 5.—The body and tail of the pancreas are notably enlarged in this patient with hemorrhagic pancreatitis. The pancreas has a lower density (more dark) than normal, presumably due to edema. The gallbladder (G) is also enlarged.

Figure 7.—A carcinoma produced this focal enlargement of the head (H) of the pancreas. Note the body and tail are also in this cross-section, and appear normal.

portion of the duodenum can otherwise simulate the body of the pancreas, but the transverse duodenum lies posterior (dorsal) to the SMA, between it and the aorta. The head of the pancreas is not so conveniently identified. Its margins often blend with the second portion of the duodenum and the inferior vena cava. When a doubt exists about the precise size and contour of the head of the pancreas, a repeat scan following the ingestion of a dilute solution of iodinated oral contrast material usually resolves the question by outlining the lumen of the second portion of the duodenum lying just lateral to the pancreatic head (Figure 4). On rare occasion intravenous injection of iodinated urographic contrast material has been necessary to identify the lumen of the inferior vena cava lying dorsal to the head of the pancreas.

Experience with CT scans of the pancreas in many normal patients is necessary to learn the normal variations in size and contour of this organ. In general, the organ tends to gradually increase in size from tail to head, and any impression of enlargement of a specific portion must take into account the appearance of the other portions. In a supine scan any portion of the pancreas with an anterior-posterior dimension greater than ⅔ the transverse diameter of the adjacent vertebral body should be suspected of enlargement.[4]

Acute pancreatitis results in a diffusely enlarged gland with an attenuation coefficient or CT number slightly less than normal (Figure 5). Pseudocysts are readily seen as round or oval, well-circumscribed zones of a notably reduced CT number (Figure 6). A calcified rim or diffuse pancreatic calcification of chronic pancreatitis is often associated. Intravenous injection of iodinated contrast material usually helps enhance the visualization of the low density center of a pancreatic pseudocyst.

In those cases of pancreatic carcinoma diagnosed by CT usually there has been shown a localized area of enlargement (Figures 7 and 8), although in a minority a more diffuse increase in size has been shown.[3-5] Some have had poorly marginated low density zones within them, representing areas of necrosis, and many have obliterated the normal fat plane posterior to the gland. It is possible that a focal area of enlargement secondary to inflammation could simulate a neoplasm on the CT scan, but clinical features will

Figure 9.—The branching, low density structures in the liver represent dilated intrahepatic bile ducts (B).

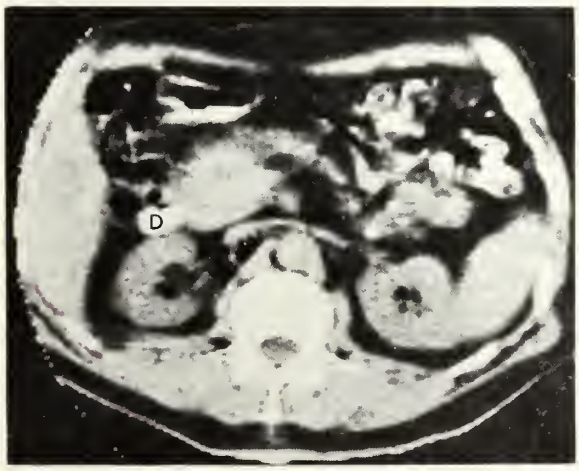

Figure 8.—Another carcinoma in the head of the pancreas. Oral contrast material fills some of the bowel, including the duodenum (D) lateral to the pancreatic mass.

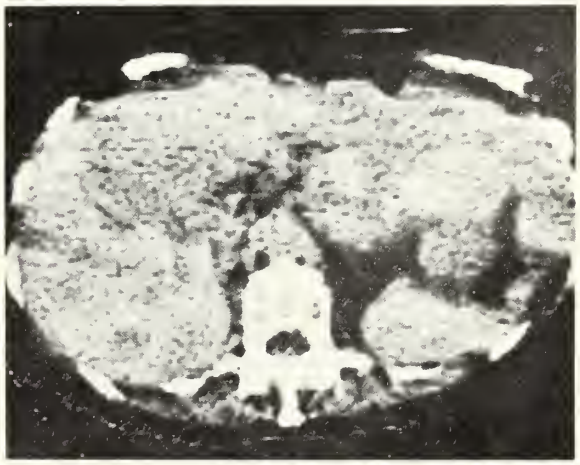

Figure 10.—Liver metastases. Both the right and left lobes of the liver contain multiple small and large areas of decreased density.

often suggest the correct differential diagnosis. Clearly pancreatic tumors too small to alter the expected size and contour of the pancreas may remain undetected. Unfortunately there is no reliable difference in CT attenuation coefficient between pancreatic carcinoma and normal pancreatic parenchyma.

Liver

CT of the liver has been used mostly to evaluate unexplained jaundice and to search for single or multiple mass lesions. Etiologic diagnosis of obstructive jaundice can be made when dilated intraheptic biliary radicles are visualized (Figure 9). They are characterized by low density zones within the liver—curvilinear near the hilum, horizontal in the left lobe and spherical in the right lobe (where they are seen end-on).[3-6] They are visualized only because the attenuation coefficient of bile is lower than that of normal liver parenchyma. Unfortunately the normal portal venous tree, coursing through the liver adjacent to the biliary radicles, occasionally produces a CT image identical to that observed with dilated biliary ducts. Injection of intravenous urographic contrast material enhances visualization of biliary ducts by perfusing the extraductal tissues, while it obscures the portal venous structures by perfusing them and elevating their density to a level near that of the surrounding parenchyma.

Among the questions yet to be answered are: (1) the degree and duration of obstruction necessary before dilatation of the intrahepatic ducts occurs, (2) the degree of dilatation necessary before it can be imaged by CT and (3) the temporal relationship between dilatation of the common

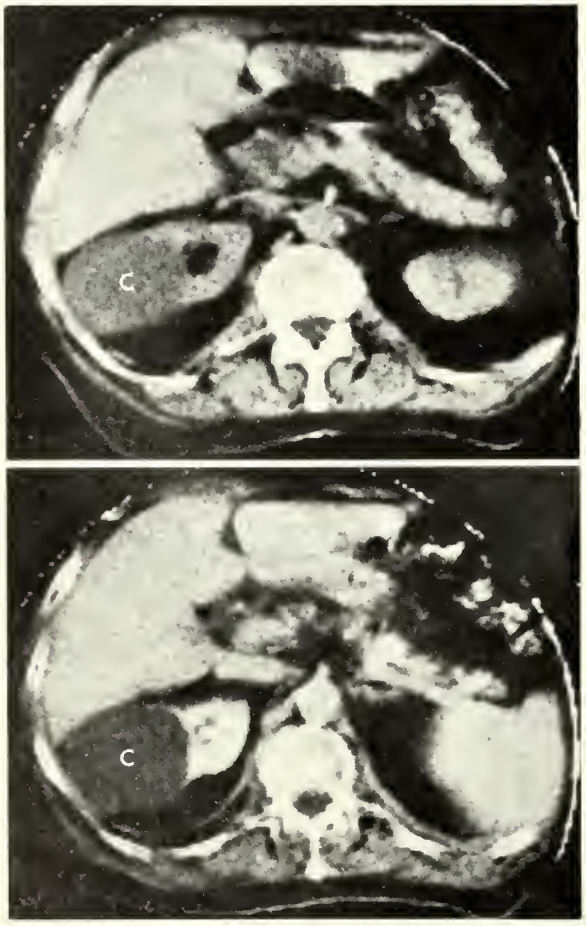

Figure 11.—Upper, a cyst (C) in the lateral aspect of the right kidney had a density reading similar to water. **Lower,** intravenous contrast material increases the density of the renal parenchyma, but not that of the cyst.

Figure 12.—The normal retroperitoneal structures are usually well outlined by fat. Note the symmetrical psoas muscles just lateral to the vertebral body.

Figure 13.—The right psoas muscle is much larger than the left, and contains a low density core within it (A). A pyogenic abscess was subsequently drained at surgical operation.

bile duct and of the intraheptic bile ducts. I have seen one case of an obstructed, dilated common bile duct with intrahepatic ducts of normal caliber in a patient with liver cirrhosis, and one case of dilated intrahepatic ducts not seen on a 2½ minute scanner. Accurate delineation of dilated bile ducts has also been reported with recent advances in gray-scale ultrasonography. It will be important to determine the sensitivity and specificity of this finding using these two noninvasive modalities.

CT evaluation of the liver should provide a rational first step in the medical evaluation of unexplained jaundice. If dilated ducts are seen on the CT scan, a percutaneous transhepatic cholangiogram using the small caliber needle technique should follow in order to confirm the diagnosis and locate the precise site of obstruction. Frequently the site of obstruction can be deduced, especially if a mass is shown in the head of the pancreas. If dilated ducts are not shown by CT, conservative medical therapy for presumed nonobstructive disease can be elected, or an endoscopic retrograde cholangiopancreatogram can be done in some cases.

CT of the liver shows mass lesions which possess attenuation coefficients sufficiently different from normal liver (Figure 10). When such differences occur, lesions that are smaller and deeper than those seen on conventional radionuclide liver scans can be identified. Sometimes, however, very large lesions easily seen on isotopic scans are not visualized by CT because their density is only slightly different from normal parenchyma. Intravenous injection of iodinated contrast material can be used to increase the CT number of normal liver and thus enhance visualization of low density lesions. However, a precontrast examination of the liver must never be omitted because occasionally a low density vascular lesion will be obscured by contrast injection.

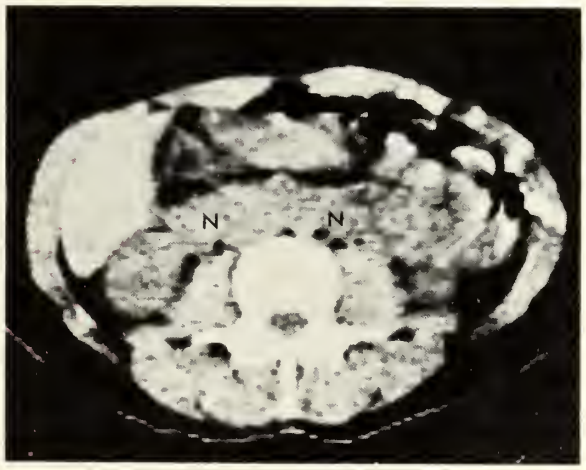

Figure 14.—A mantle of tissue (N) completely traverses the prevertebral space, obscuring the normal borders of the aorta and inferior vena cava. This pattern is characteristic of diffuse retroperitoneal lymphadenopathy.

Even if a radionuclide liver scan shows a filling defect, CT scanning can determine which defects are due to cysts and which to simply an anatomic thinning of the liver. CT scans showing pronounced diminution of liver density in the presence of fatty infiltration, or a notable increase in liver density in hemochromatosis, have also been described.[3-6]

Kidney

Computed tomography is useful in evaluation of three types of renal abnormalities seen at urography: (1) renal mass, (2) nonfunctioning kidney and (3) abnormal renal axis.

Renal cysts present a CT image of a mass having a CT number near that of water, a number that does not change following intravenous injection of urographic contrast material (Figure 11).[3] The CT number of a renal carcinoma is close to that of the normal renal parenchyma, and it increases in density with contrast injection, though not to the same degree as the adjacent normal tissue. Solid renal masses other than cancer presumably will show the similar CT characteristics; further experience is necessary to ascertain whether or not any differences will reliably distinguish renal cancer from other noncystic lesions. As of the time that this report is being presented, the accuracy of CT in distinguishing cysts from solid lesions has not been established. I have seen one case of multiple benign, hypervascular angiomyolipomas in which the correct diagnosis was made by CT because of the readily apparent fatty nature of the tumors.

The role of CT in routine evaluation of renal masses will probably be a limited one in places where high quality ultrasonography is present, because the diagnostic accuracy of the latter can be as high as 95 percent. CT will probably be reserved for those renal masses in which the ultrasound pattern is indeterminate in type, or where the sonogram is technically suboptimal. Because the density of any mass depends on whether all or a part is included in the volume of a given picture element, it is possible that very small in-

trarenal lesions will not be confidently differentiated by CT evaluation.

A kidney nonfunctioning at urography can be easily evaluated by CT. Hydronephrosis presents a characteristic image of an oval, water density mass in the renal sinus. Even if the diagnosis of obstructive hydronephrosis is apparent at urography, CT can be used to determine whether a mass is present at the site of obstruction. We recently examined a hypertensive child with elevated vanillylmandelic acid (VMA) levels whose urogram showed an obstructed ureter near its entrance into the bladder. A 2 cm oval mass was shown on the CT section taken at the site of obstruction. It proved to be an extra-adrenal pheochromocytoma.

One of the most perplexing problems encountered during urography is that of an abnormal renal axis, with the kidney lying in a vertical orientation or with the upper pole more lateral in position than the lower pole. Such a finding usually raises the possibility of a paraspinal retroperitoneal mass, but previously this could lead to an often unrewarding series of diagnostic maneuvers. A CT scan centered on the site of altered renal axis safely leads to a rapid diagnosis. Frequently a soft tissue mass is easily identified, at other times just a large amount of retroperitoneal fat lies between the spine and the kidney.

Retroperitoneal Space

More than any other area of the body, the retroperitoneal space is uniquely and spectacularly imaged by CT scanning (Figure 12). The pancreas, of course, lies at the cephalic end of the retroperitoneum, and we have already described the salient features of CT pancreatic scanning. The remaining portion of the retroperitoneum is frequently the site of neoplasms, abscesses and hematomas (Figure 13), all of which are notoriously difficult to diagnose by conventional imaging techniques. The aorta, inferior vena cava and both psoas muscles are usually well outlined by surrounding fat, and any significant amount of abnormal tissue is usually readily apparent on the CT scan. Even the CT demonstration of a normal retroperitoneum can be very useful in a patient with unexplained abdominal or back pain.

Lymph nodes are normally seen as very small structures of variable number surrounding the aorta and inferior vena cava, many lying between the spine and the great vessels. When these nodes become grossly enlarged, a CT diagnosis of retroperitoneal adenopathy is easily made, particularly when the nodes occur in the normally clear space between the aorta and left psoas muscle (Figure 14). But current resolution of CT scanners does not allow diagnosis of infiltrative disease of normal sized nodes. Although negative findings on CT scan do not exclude significant disease in normal sized nodes, enlarged retroperitoneal nodes shown in patients with known or suspected lymphomas may in selected cases obviate lymphangiography. Scans following lymphangiography in patients have shown that the lateral extent of dispersion of the lymphangiographic contrast material in lymphomatous nodes often underestimates the true lateral extent of the abnormal tissue.

Clearly our general approach to the diagnosis and evaluation of space occupying lesions is in the process of being revolutionized by the noninvasive computerized tomography.

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Important Advances in Clinical Medicine

Epitomes of Progress—Ophthalmology

The Scientific Board of the California Medical Association presents the following inventory of items of progress in ophthalmology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in ophthalmology which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Ophthalmology of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, California Medical Association, 731 Market St., San Francisco, CA 94103

Vitrectomy

VITREOUS has long been considered the enemy of ophthalmic surgeons. Only a few years ago, one's skill was measured in no small degree by the ability to avoid contact with the vitreous, and the vitreous cavity itself was "off limits" to surgical intervention. Recently, this all has changed, and changing attitudes and capabilities for dealing with the vitreous are revolutionizing intraocular surgery.

In 1968 Kasner and co-workers reported the successful removal of nearly all diseased vitreous from an eye with primary amyloidosis, using his so-called open sky technique. This opened the door for new surgical techniques to remove vitreous and intraocular strands in a variety of diseases. It quickly became evident that the open sky technique had several hazards: the lens had to be removed, resulting in aphakia; there were possible further complications of the large corneal section or corneal graft; the iris was irritated and frequently severe inflammatory reaction resulted; instruments for the procedure were usually inadequate and too large; traction on vitreous during the cutting near the iris plane was unavoidable, and collapse of the eye prevented adequate visualization of certain areas of the posterior segment.

In 1971 Machemer and associates reported their initial results on the pars plana approach to vitrectomy. Pars plana vitrectomy was developed with the following objectives in mind: To eliminate the anterior segment problems seen in open sky vitrectomy, the anterior segment should be left intact and the vitreous should be removed through a very small incision at the pars plana. To improve on instrumentation, only one miniaturized multifunction instrument should be introduced into the eye. This instrument would have to

cut and remove diseased vitreous from the eye as well as simultaneously replace the removed vitreous with clear fluid. Fiber optics were chosen to provide precise and effective internal illumination. To achieve maximum control over intraocular manipulations the instrument should be observed through the pupil under the high magnification, stereopsis, and upright imagery of an operating microscope.

Many medical centers have enthusiastically adopted procedures for removal of opaque vitreous through a pars plana incision with an instrument combining suction, cutting and infusion of a replacement solution. The most common indication for vitrectomy has been the presence of a long-standing severe vitreous hemorrhage in eyes with proliferative diabetic retinopathy.

Vitrectomy often is followed by rapid, substantial improvement in visual acuity from low preoperative levels, and these results have been sufficient to convince most clinicians of the value of the procedure without a controlled study. To document the validity of this impression, the National Eye Institute gathered and pooled data on the experience of six clinics at which vitrectomy is done. The data show that over 41 percent of 145 eyes which had visual acuity of less than 5/200 and in which severe vitreous hemorrhage had been present for a year or more achieved visual acuity of 20/200 or better four to nine months after pars plana vitrectomy. Although no corresponding control data are available, data from the Airlie House Symposium on the Treatment of Diabetic Retinopathy, as reanalyzed by Caird and Draper (unpublished data), show that in a group of 58 eyes with visual acuity of less than 20/200 and vitreous hemorrhage severe enough to preclude observation of the fundus, the rate of recovery to 20/200 or better after one year without treatment was only about 8 percent.

In most of the large series of reported results of pars plana vitrectomies in the literature since the introduction of the pars plana technique, about 50 percent have been for the late complications of proliferative diabetic retinopathy. A new prospective, randomized, controlled clinical trial of vitrectomy in the treatment of diabetic retinopathy has been initiated by the National Eye Institute. The study's purpose is to compare vitrectomy done soon after severe vitreous hemorrhage in eyes with proliferative diabetic retinopathy and vitrectomy done a year after the occurrence of hemorrhage, as is now generally practiced. The study's protocol has been prepared and patient enrollment will soon begin.

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Intraocular Lens Implantation

THE MODERN HISTORY of intraocular lens implantation began on November 29, 1949, when Harold Ridley inserted the first intraocular lens. Although complications related to use of this type of lens occurred far too frequently and its use was soon abandoned, numerous intraocular lenses were developed and used clinically in the years thereafter. The overall results and complications of intraocular lens implantation may be assessed by reviewing Binkhorst's cumulative experience with 795 Binkhorst iris clip lens implantations and 170 Binkhorst iridocapsular lens implantations done on 717 patients between 1958 and 1972.

Disadvantages of intraocular lens implantation relate to the increased likelihood of surgical complications associated with a more complex procedure; the tendency of surgical and immediately postoperative complications to have a more profound effect on an eye with an intraocular lens; the occurrence of complications directly related to the lens, such as lens dislocation; the occurrence of late corneal dystrophy, the incidence of which is probably greater than that following conventional cataract surgical procedures; the occurrence of macular cystoid degeneration in an incidence that may be greater than that following conventional cataract surgical operation, and possible late complications related to alterations in or toxicity of intraocular lens implant materials.

From a careful evaluation of the advantages and disadvantages of intraocular lens implantation, the indications and contraindications may be derived. This topic, however, is controversial, because appropriate scientific data on the long-term

results of cataract extraction with intraocular lens implantation and comparative data on the results of cataract surgical procedures without lens implantation are not available. In general, intraocular lens implantation is indicated when:

- Cataract extraction is warranted according to the usual ophthalmic surgical criteria,
- The patient is 65 to 70 years of age or older,
- The patient is unable to use a contact lens satisfactorily,
- There is no specific contraindication to intraocular lens implantation,
- The patient desires intraocular lens implantation based on fully informed consent.

These guidelines should be considered general principles rather than rigid factors. As experience and scientific information increase, these guidelines may be modified. Moreover, special circumstances may warrant lens implantation in patients at a relatively early age, for example, a cataract in a patient with poor manual dexterity due to arthritis, tremor or paralysis.

Contraindications to intraocular lens implantation at this stage of scientific knowledge include the following circumstances:

- The patient has only one useful eye,
- There is a history of uveitis or retinal detachment,
- The patient has rubeosis irides or severe iris atrophy,
- The patient has proliferative diabetic retinopathy,
- Complications at the time of surgical operation, such as severe hemorrhage or a persistently large pupil make implantation inadvisable.

These contraindications, just as the foregoing indications, are general principles. They are not comprehensive, and no combination of indications and contraindications can substitute for professional judgment. Finally, it must be emphasized that many facts regarding intraocular lens manufacture, clinical use and long-term results are not available. Recognizing these gaps in knowledge, intraocular lens implantation is the subject of intense professional attention and scientific investigation.

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Current Concepts of Proliferative Diabetic Retinopathy Management

DIABETIC RETINOPATHY is one of the leading causes of blindness and visual disability in the United States. It can be classified into nonproliferative and proliferative retinopathy. The proliferative stage of the disease is characterized by new vessel growth on the surface of the retina, or optic nerve. It can also be associated with fibrous tissue proliferation, vitreous hemorrhage and tractional retinal detachment. These changes lead to severe degrees of visual loss.

Photocoagulation treatment of proliferative retinopathy has gained widespread acceptance in ophthalmology since 1959. There have been numerous studies of photocoagulation treatment for proliferative diabetic retinopathy in the past 15 years. However, most studies have failed to adhere to the most basic principles of clinical trials, that of random assignment of eyes to treatment or control groups, and comparison of treated and untreated eyes. Moreover, the results of the controlled studies that were done were not valid due to the small number of patients involved. Consequently, results of these studies have been inadequate to evaluate fully the effectiveness of photocoagulation on proliferative diabetic retinopathy.

In 1971 the Diabetic Retinopathy Study (DRS) began under the sponsorship of the National Eye Institute. This randomized, controlled clinical trial involved more than 1,700 patients enrolled in 15 medical centers. Each DRS clinic followed standardized procedures and data were collected and analyzed centrally. Patients with visual acuity of 20/100 or better in each eye and evidence of proliferative retinopathy in at least one eye, or severe nonproliferative diabetic retinopathy in both eyes were eligible for enrollment. Patients were treated with either argon laser or xenon arc photocoagulation. One eye was treated and the other eye followed as a control. The selection of the eye for treatment and the modality for treatment was done randomly.

The results of the study as of September 1975 showed evidence that photocoagulation treatment as carried out in the DRS (extensive scatter photocoagulation and focal treatment to new vessels) was effective in reducing the incidence of severe visual loss (the occurrence of visual acuity less than 5/200 for two consecutively completed four-month follow-up visits) from 16.3 percent

in all untreated eyes to 6.4 percent in treated eyes after two years of follow-up. Based on these findings and the evaluation of various sub groups of diabetic retinopathy in the DRS, treatment is now being recommended for untreated eyes if the following conditions are present:

- Moderate to severe new vessels on or near the optic disk,
- Mild new vessels on or near the optic disk with associated vitreous or preretinal hemorrhage,
- Moderate to severe new vessels elsewhere on the surface of the retina if vitreous or preretinal hemorrhage is present.

It is apparent that while there is no cure for diabetic retinopathy, photocoagulation treatment applied to certain stages of this disease, according to the DRS protocol, is effective in reducing the incidence of severe visual loss. It should be stressed that the current recommendations for treatment are based on a preliminary report of two years' follow-up data after treatment. Evaluation of all patients in the study will continue and further analysis of the findings will be done to determine the long-term effectiveness of photocoagulation therapy, comparison between xenon arc and argon laser treatment, and the effect of this procedure in eyes with other degrees of retinopathy.

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Visual Evoked Response

VISUAL EVOKED RESPONSE (VER) testing has been one of the most exciting clinical tools to be developed from neurophysiologic research in recent years and has provided us with an objective method of identifying abnormalities of the afferent visual pathways. More than thirty years ago it was shown that regularly repeated flashes of light before the eyes produced evoked responses in the electroencephalogram (EEG) recorded over the occipital cortex. However, in only a small number of people was there a visual evoked response because usually the response was so small it was lost in the random noise of the EEG (amplitude of largest VER waveform is only about 20 microvolts as compared with 500 microvolts for the electroretinogram (ERG). It was not until early in the 1960's that computers were developed that permitted averaging of an evoked response that was time locked to the stimulus. Thus, if a light flash was repeated rapidly 100 times before the eyes and the occipital EEG was recorded by a computer-averager, the common time-locked evoked response was added together to produce a clear wave form while the random EEG noise was slowly approximated to zero.

The stimulus often used to produce a VER is one hundred white flashes of light from a photostimulator. However, other investigators find that a more reproducible response is produced to a rapidly reversing black and white checkerboard pattern. Still other investigators use a straight pattern flash without pattern reversal. Thus one of the problems when reading VER literature is to know what stimulus is used (that is, flash, pattern reversal or pattern flash) and what that laboratory considers normal response.

The clinical usefulness of VER testing was heralded by Richey and co-workers (1971), Namerow and Enns (1972), Feinsod and associates (1973), and Halliday and associates (1973). They showed the frequent findings of an abnormally prolonged latency or an abnormal waveform in patients with multiple sclerosis who had no historical or clinical signs of visual system involvement. Often the abnormal VER will confirm a diagnosis of multiple sclerosis and prevent further expensive and painful neurologic testing.

VER has been clinically useful in several other ways. Malingerers who claim blindness in one or both eyes will produce a normal VER objectively refuting the patient's claim. On the other hand patients with posttraumatic subjective visual complaints without objective ophthalmologic signs may have an abnormal VER substantiating their complaints.

VER has been used to monitor optic nerve function during surgical removal of a pituitary adenoma compressing the chiasm. During surgical operation restoration of the normal VER pattern with removal of the tumor allowed the neurosurgeon to know when he had adequately decompressed the chiasm. Postoperatively the patient had a return to normal vision.

VER to an appropriate pattern reversal screen 6° in size has been shown to measure macular function and may be used to follow various forms of macular degeneration. VER abnormalities

shown by comparing homonymous field quadrants have been used to identify objectively field defects in patients with glaucoma. Rapid, objective refraction using VER has been possible and may prove clinically useful in the future.

Recently, waveform has begun to take on new importance in VER analysis. Attempts currently are being made to develop computer models of normal and abnormal waveforms. In addition, the use of color with various stimulus measurements is being investigated actively.

Some of the clinical applications to which VER has been applied are in the embryonic stages of development. The potential list of clinical applications of VER is endless. How many of these applications ultimately prove to be helpful remains to be seen. One fact seems certain—VER is here to stay as a valuable neuro-ophthalmologic tool.

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Advances in Glaucoma Management (Including Laser Treatment)

GLAUCOMA is an optic neuropathy associated with an elevated intraocular pressure leading to cupping of the optic disc and a loss of visual field. Therapy in glaucoma is aimed at reducing the intraocular pressure by decreasing the flow of fluid into the eye or by increasing the flow rate of fluid leaving the eye. Medical therapy, including the use of eye drops and orally given medications, are the first line of defense in glaucoma management. When medical therapy fails to halt the progression of nerve damage and field loss, surgical therapy is undertaken. As medical therapy is intensified or surgical therapy applied, the risks and complications of therapy increase and can affect not only the eye, but the body in general. There is a constant search for therapies that have increased effectiveness and safety in the management of glaucoma.

Examples of some of the new techniques include continuous ocular therapeutic systems. These devices contain medications that are metered out a small amount at a time resulting in drug effect without the transient overdose associated with the pulsed delivery of drugs such as with the use of eye drops. This results in a more even effect, lowered total dose, and reduced local and generalized side effects of the medication. However, this form of therapy cannot be used in all patients.

New classes of drugs that work in new ways also offer hope for the glaucoma patient. These include beta-adrenergic blocking agents and derivatives of the marijuana plant. Studies of these drugs are still investigational and thus such medication is not generally available but results of preliminary studies are certainly encouraging.

Microsurgical techniques have increased the safety of surgical operation for glaucoma by allowing better control during the operation. Microsurgery also has increased the variety of operations the surgeon can use thereby making it possible to fit a specific operation to a specific patient.

Laser therapy for glaucoma has been used for angle closure or sudden onset glaucoma as well as open angle glaucoma. A finely focused beam of laser light can be used to create a hole in the iris thus avoiding the need for surgical procedures in patients who are candidates for the usual operation of peripheral iridectomy. Investigations also are underway using laser in the treatment of open-angle glaucoma and in neovascular glaucoma associated with diabetes. In both of these latter cases, the laser beam is directed to the area where fluid normally leaves the eye, the trabecular meshwork.

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Retinitis Pigmentosa

RECENT YEARS have seen an increased interest in both basic science and clinical aspects of the genetically diverse group of diseases collectively known as "retinitis pigmentosa."

Basic research of current interest centers around genetic studies, the search for chromosomal markers and animal chimeric studies whereby, through intricate microsurgery, retinal tissues from both normal and dystrophic breeds of embryonic mice are joined to produce a hybrid retina. The resulting retina contains both genotypic varieties in one tissue. Further studies include biochemical investigations into visual pigment synthesis, the interaction between retinal pigment epithelium and receptor cells for both normal and dystrophic animals, and retinal enzyme characteristics of selected genetically deficient animals.

Clinically, the value of a systematic approach to data accumulation and computer assisted data analysis has become increasingly recognized. Several university centers, including the University of California, Los Angeles, have established registries of retinitis pigmentosa patients. Data have been collected prospectively, but may be reviewed retrospectively at any chosen time.

Several interesting points have come to light:

- Retinitis pigmentosa starts without intraretinal pigmentary deposition. This may account for the fact that the clinical signs and symptoms are far advanced at the time that the ophthalmoscopic diagnosis is made. Thus, instead of being a rare or atypical form of the disease, the nonpigmented state is universal in the disease's early stages, and correlates with less severe functional loss as measured by visual acuity, dark adaptation function and peripheral visual field constriction. With the passage of time, pigmentation typically appears, making the clinical diagnosis easier. The bone-corpuscle, or cobweb pigmentation is itself of little significance. In some relatively rare instances, intraretinal pigment deposition fails to occur even after 20 or more years of advanced clinical disease. Such cases were presumably the ones that Leber referred to as "retinitis pigmentosa sine pigmento."
- Accumulated data can be reviewed with respect to the rate of disease progression as a function of the duration of subjective night blindness. X-chromosome linked retinitis pigmentosa appears to be the most severe and rapidly progressive form of the disease, with the worst prognosis for vision. Dominantly inherited retinitis pigmentosa may frequently show the mildest functional loss, but variable genetic expressivity accounts for cases of dominant retinitis pigmentosa in which there are severe functional impairment and rapid progression.
- Central visual impairment, implying cone involvement, or at least retinal pigment epithelial involvement underlying cone receptors, occurs with greater frequency than previously appreciated. In one series, 48 percent of retinitis pigmentosa patients had Snellen visual acuities of 20/50 or less in one or both eyes at the time of the initial examination. The mean age of the centrally impaired group was only 38 years. Previously held optimism regarding the preservation of central vision until late in life must be reexamined in view of these figures.

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Increasing the Accuracy of Operation for Strabismus

ALMOST EVERY CASE of strabismus is some mixture of abnormal restrictions to eye movement, abnormal reflex patterns which control binocular vision and abnormal innervation to the extraocular muscles. While these can be sorted out by special tests in some adults, it is not possible to carry out such investigations in most of our strabismus patients, children. Consequently, operation for strabismus is frequently inaccurate and a reoperation rate of 20 to 50 percent is the result.

Ability to adjust or "fine-tune" the surgical result substantially increases the accuracy of results and reduces the incidence of reoperations in difficult cases where ordinary guidelines are lacking. This is carried out by three techniques: The first is to hold the eye in proper alignment position by some "stay" sutures, much as a broken arm is held in position for optimum healing.

These sutures then can be tightened or loosened to move the eye into optimum postoperative healing position. The second is to lengthen or shorten the sutures attaching the muscle to the eye under mild sedation on the first postoperative day. Up to 10 degrees of recorrection have been obtained in this manner. The third approach is to operate under local anesthesia and adjust the muscle position at the time of operation, until alignment of the eyes is correct. This third technique is obviously only for use in cooperative adults.

It must be emphasized that judgment in many ordinary cases is thoroughly sufficient and the additional discomfort and trouble associated with these techniques is not warranted. In difficult and unusual cases, however, they represent a chance to fine-tune the operation and therefore avoid reoperation at a later time.

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EDITORIALS

A Problem Solving Process for Health Care

PHYSICIANS have developed a most effective technique which they use every day to solve problems in patient care but which they seem seldom if ever to apply to the larger problems of health care itself. Yet at least in principle, the process seems almost uniquely fitted to address many of these problems. In both patient care and health care the situation is likely to be a changing one, and often actions must be taken based upon the available information which may be something less than adequate. Given the many problems in health care confronting the profession, it would seem reasonable to examine the basic problem solving technique that medicine has developed for patient care and that is familiar to every physician, to see if it might be a practical way to approach some of these problems.

A brief description of this problem solving process might be in order. First the problem is identified and then defined as precisely as is possible or necessary. The chief complaint introduces the problem, and this is followed by gathering information about how it developed and its characteristics from the patient and others who know about it, through the history. In the physical examination the physician actually takes a firsthand look at the problem and this produces some objective information. Laboratory data and other information are then acquired which usually provide some measurement of it. All of this identifies and defines the problem. The next step is to form an opinion of what is wrong, what is likely to happen and what are the options—what can be done about it. This is usually done primarily by the physician and involves the application of knowledge and experience, but others including consultants of various kinds are often involved. Then a decision as to a course of action is reached. Here there is always participation by the physician, but except in the most emergent circumstances all the others appropriately concerned, and particularly the patient, are also involved in deciding what should be done. A plan of action is decided upon, and is then implemented by all concerned in accordance with the agreed-to plan. As new information is acquired and progress is observed, there is prompt correction or refinement of the definition of the problem, the data base and the course of action itself. This is a particular characteristic of this technique and is essential for effective problem solving in fluid or changing situations. The process continues until either the problem is solved or a reasonably acceptable steady state is reached. It is worth noting that although the physician may orchestrate this whole process, give advice, or even be an advocate of one or another course of action, there must not only be informed consent but also the active and, if possible, the willing participation of many others if the problem is to be dealt with to the general satisfaction, or even at all.

The important elements of this process seem to be (1) involvement of all who should be involved; (2) a means of getting a definite hold on a problem and some measure of it; (3) a focus on what is wrong, what is likely to happen and the options to deal with it; (4) participation of all those properly concerned in the decision so that all will understand what needs to be done, have agreed to it and be willing to do their part to carry it out, and (5) the quick correction or refinement of each step in the process as experience accrues and new information becomes available.

If one extrapolates the use of this process by a physician in dealing with a patient's problem to its use by the medical profession in approaching a larger problem in health care, it may be seen that the elements necessary to solve these two kinds of problems are much the same. It is suggested that perhaps the time has come for medicine, and even government, to explore the use of this eminently successful and practical problem solving process to address some of the larger problems of health care. Suitably adapted, it just might work.

—MSMW

Cancer and the Immunity System—1977

THE CRUCIAL ISSUE in harnessing the powerful immunologic machinery to fight cancer in humans is whether cancer cells have antigens at their surface that can be recognized as being foreign to the host.[1] If this is the case, ingenious and effective new methods can be developed to provide a telling, specific assault on malignant cells. By contrast, if most human cancers lack, entirely, antigens foreign to the host, the immunologic approach to cancer will remain nonspecific and the science of harnessing immunologic processes to fight cancer would have to be developed with focus toward understanding and manipulating the biologic amplification mechanisms and immunologic effector processes without the advantage of specifically directed assault.

In the fine review of progress toward immunotherapy of cancer in this issue, Holmes and coworkers have summarized the background of current understanding and progress made to date in developing an immunotherapy of cancer. Although not yet spectacular, results already indicate that immunotherapy of some types of cancer is beginning to work. One most impressive achievement has been the capacity to use contact allergic reactions fired off in the vicinity of skin cancer to treat and even prevent skin cancers from occurring in susceptible persons.[2] Local injections of bacille Calmette Guérin (BCG) vaccine to induce regression of most melanomas treated has proved effective enough to become a clinically useful tool. Even more encouraging is that, following such local treatment, an apparent immune reaction leads to regression of distant skin metastases of the malignant melanoma in some instances. Treatment using BCG infection of skin and systemic BCG as adjunct to surgical operation and chemotherapy has apparently improved the outcome of melanoma in some series. Intrapleural injections of BCG appear, from a well controlled clinical trial, to prolong the disease-free interval in relatively early lung cancer.[3] Prolongation of life and improvement of remissions in lung, breast, colon and other cancers in advanced stages by treatment with BCG, Corynebacterium parvum or levamisole have been coupled with chemotherapy or irradiation therapy to apparent advantage for patients with cancer.[4-7] Active immunization with neuraminidase-treated allogeneic leukemic cells has appeared to improve to a notable extent the outlook of acute myeloid leukemia in some studies.[8] Similarly, pseudomonas vaccine with or after chemotherapy has apparently yielded long-term survivors of acute leukemia where chemotherapy alone has usually failed.[9] As a beginning these results are encouraging.

One basis for current optimism about the immunological approach to cancer derives from a strong experimental base which shows that chemically-induced cancer, cancer caused by physical agents, cancer caused by viruses and spontaneous cancers of animals often possess readily identifiable antigens which are foreign to the host and can be recognized as such by the immunological system when it has been properly stimulated.[1,10] In experimental systems, the immunologic machinery has been harnessed repeatedly to prevent, treat or even cure cancer, sometimes even without assistance of other therapeutic modalities.[11] A sixty-four dollar question is whether spontaneous tumors of either animals or man regularly possess antigens foreign to the host.[12] Without doubt, some spontaneous tumors do possess such antigens,[13] but progression of tumors involving a process of immunological selection or other escape mechanisms may render the antigens on the surface of many spontaneous cancers either very weak or apparently nonexistent.[14-16] If this is the case, then the problem of developing immunotherapy or immunoprophylaxis of cancer becomes much more difficult and less susceptible to the focus of specificity.

It is encouraging for the immunologic approach to cancer that studies with human tumors suggest that antigens foreign to the host and characteristic of the tumor have been described.[16-22] Few, if any, of the tumor antigens described for human cancers have thus far been defined sufficiently in precise, critical serological analyses. It is clear that in Burkitt's lymphoma, as in nasopharyngeal carcinoma, tumor-specific antigens induced by the virus that is most likely responsible for these diseases are present on the cancer cell.[23] In this vein, the recent work of Old and his team on serology of human malignant melanoma seems especially important.[24,25] From their studies comes the most impressive evidence for tumor-specific

antigens on human malignant melanoma. One antigenic class appears to be specific for the cells of individual melanomas and is recognizable only by autologous antibodies.[24] Another class appears to identify certain but not all melanomas.[25] Thus, a serological classification of melanomas and other cancers can now be launched on a sound basis. Such definition of cell surface antigens on melanoma cells could pave the way to chemical definition and purification of these tumor-specific antigens as has been achieved for H_2 and HL-A antigens that exist on the surface of most normal cells. Similarly, exciting new information indicates that illegitimate blood group antigens may exist on the surface of some epithelial tumor cells, such as the cells of breast and stomach cancer. This most important information comes from studies of Springer and co-workers,[26,27] who have identified the Thomsen-Friedenreich antigens of the MN blood group system on breast cancer, and Levine[28] who has recognized that illegitimate antigens of the P system may occur on gastric cancer. Dr. Levine's analysis of a fascinating case[28] further suggests that cytotoxic antibodies directed against the blood group antigens may have contributed to clearing of residual malignant cells and as such reflects a possibility that might be useful for cancer therapy.

These new definitions could surely be the opening wedge that could lead to effective immunologic approaches to earlier diagnoses, effective immunotherapy, immunologically directed chemotherapy and incisive cancer immunobiology. If this is true, dreams derived from laboratory cancer immunology could become a vital reality for some types of cancer in humans. However, much difficult scientific work lies ahead.

Immunotherapeutic measures currently in use can be likened to kicking a broken television set when we want to repair it. It is encouraging that such crude approaches as have been used to date can work even a little bit. The future, however, holds promise of precise chemical management of immunostimulation, real understanding and better control of immuno-effector therapy, specific immunotherapy and immuno-directed chemotherapy. Precise science, carefully controlled trials and a highly critical attitude are necessary for steady progress.

A crucial experiment of nature in this field is, it would seem, represented by the widely disseminated cancer which derived from inadvertent transplantation of cancer along with kidney allografts. The allotransplanted tumor was given license to survive in the allogeneic host by the chemical suppression of immunological function. In two separate instances, the powerful immune reaction undoubtedly directed toward alloantigen on the surface of the tumor cells resulted in complete elimination of the trillions of disseminated foreign tumor cells.[29] This means that human cancer can be eliminated from the body by immunologic means even when the cancer is widely disseminated. What is needed, of course, is that through our serologic analysis of tumor antigens and the progress which is yielding ability to control immune responses of the host, we can make the body look upon weak antigens of human tumor cells as though they are strong and can thus marshal the full vigor of the immunologic machinery against the cancer. Recent progress encourages continuing efforts to develop a science devoted to this great achievement.

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Summer Preceptorships

SUMMER PRECEPTORSHIPS for medical students are nothing new. But what is new is the need for many more students than before to garner some dollars during their summers to help them meet some of the ever-rising costs of getting a medical education. Elsewhere in this issue is an account by a second-year medical student of his most worthwhile experience as a summer preceptee, and of his gratitude for being taken into the home of his preceptor and so being able to save quite a few extra dollars for his needs in the coming academic year.

It is evident that both student and preceptor gained much from this experience. But beyond this, it is an expression of one of the oldest and grandest things in the Hippocratic tradition of medicine, ". . . to teach them this art, if they shall wish to learn it, without fee or stipulation; and that by precept, lecture, and every other mode of instruction, I will impart a knowledge of the art . . . to the disciples who have enrolled themselves and agreed to the rules of the profession. . . ."

Things are surely quite different here and now than they were on the island of Cos in the late 5th century BC. But the need to pass the art from preceptor to preceptee, from a practitioner who has mastered it to a student who must learn it, has not changed, and the ancient preceptor-preceptee relationship remains a valuable experience for both. Summer preceptorships are to be encouraged, and the dollars, which are more important now than they were 2,500 years ago, should somehow be found for those who need them. These experiences add an important dimension to the education of a young physician—a dimension that practicing physicians are uniquely able to give.

—MSMW

Reye's Syndrome and Ondine's Curse

THE PULMONARY CONFERENCE REPORT from Stanford in this issue includes a most elegant, comprehensive discussion, by Eugene Robin, of various pathophysiologic processes inducing hypoventilation. An almost bewildering variety of syndromes are present in patients with neurologic, airway, pulmonary, hepatic and other disease processes. I wish I could offer the reader the broadly sweeping brush of simplification, but in fact, what little I can add is further complexity.

A minor omission from the discussion and Dr. Robin's Table 1 is the role of the carotid and aortic body peripheral chemoreceptors in their response to arterial hypoxia and acidemia. More common than direct lesions of carbon dioxide chemoreceptors is loss of ventilatory drive usually transmitted by the IX cranial nerve from these glomera. Carotid bodies may be inadvertently denervated during carotid endarterectomy,[1] or deliberately excised to ameliorate asthma.[2] Chronic hypoxia gradually "blunts" its own response, and about 10 percent of the normal population is virtually unresponsive to hypoxia, suggesting that such defects are benign. More serious is damage to IX nerve roots by meningitis or movement of the brain stem. The absence of gag and laryngeal reflexes in the child subject of this report suggests IX nerve involvement, and resembles the syndrome Mitchell and I observed in a patient whose IX nerve roots were avulsed by a surgical attempt to relieve cervical cord traction

pain of platybasia.[3] She probably also had X nerve root damage, and when neglected for a few minutes, would forget to breathe, a victim of Ondine's curse. Usually, the total loss of peripheral chemoreceptor drive does not lead to respiratory failure like that seen in this child, but does induce a 15 percent rise in Pa_{CO_2} to about 46 mm of mercury, and converts the effect of hypoxia from stimulation to depression of ventilation.

The medullary carbon dioxide chemoreceptors are apparently nerve endings lying on or near the surface of the ventral medulla,[4] where one might expect them to be easily attacked by infection or toxins in cerebrospinal fluid, yet as far as I know no one has obtained pathologic evidence of such a lesion producing Ondine's curse or respiratory failure. The site of lesions inducing hypoventilation seems usually to involve the nuclei of the glossopharyngeal and vagal nerves, where the real business of regulating automatic ventilation is carried on. As Robin points out, pathways of voluntary ventilatory control are sufficiently remote from these nuclei to be spared in some patients who have lost automatic drive.

The normal balance of carbon dioxide and oxygen related drives is heavily tilted to carbon dioxide. About 85 percent of our resting or sleeping ventilation depends on stimuli from hydrogen ions in the extracellular fluid of these medullary chemoreceptors, as controlled by arterial carbon dioxide pressure (Pa_{CO_2})—provided that arterial oxygen presure (Pa_{O_2}) is greater than 80 mm of mercury. When Pa_{O_2} falls to 40 mm of mercury (75 percent saturation of hemoglobin), the tilt is reversed, and resting ventilation is multiplied by some three to five fold (at constant Pa_{CO_2}). I use the term multiplied because both human and animal experiments indicate that the effect of hypoxia multiplies rather than adds to carbon dioxide drive, or in graphic terms, hypoxia steepens the slope of the ventilatory response to carbon dioxide. Over the range we feel safe in studying in man this seems to result in a curious phenomenon: This strong response to hypoxia is essentially eliminated by a small fall of Pa_{CO_2} (about 5 mm of mercury) to what is called the apneic threshold. If a normoxic normal subject is sedated (or anesthetized), and is mechanically hyperventilated to a Pa_{CO_2} below his threshold for a few minutes, he subsequently will show either apnea or "ataxic" hypoventilation until Pa_{CO_2} climbs back to this threshold.[5] Awake subjects usually have too much overriding "wakeful" drive to manifest apnea, as noted by Robin with respect to the Plum test. The upshot of this carbon dioxide-oxygen interaction is that acute hypoxia strongly stimulates ventilation, which soon lowers Pa_{CO_2}, which then turns off the stimulus. We reach a new steady state, for example at a Pa_{O_2} of 40 mm of mercury (as if suddenly transported to 14,000 feet altitude), after Pa_{CO_2} falls about 4 mm of mercury, canceling four fifths of the hypoxic drive, leaving ventilation only marginally increased (by the fraction 40/36, or 11 percent in this example).

It remains uncertain whether very severe hypoxia can directly stimulate breathing, bypassing this carbon dioxide multiplier mechanism. Is hypoxia responsible for the terminal gasp? Can it override the inhibition of hypocapnia? Probably yes, but the evidence is rather slim. The question is relevant in a patient who, like this child, seems to have a totally flat carbon dioxide response. Clearly hypoxia becomes an impotent stimulus if it must be multiplied by zero. But what is it that causes this boy, finally, to breathe twice a minute during sleep? Why not test whether oxygen administration induces total apnea at this point? My guess is that it will, and that we stand to gain a significant insight into the ultimate defense mechanism by testing it.

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CASE REPORTS

Refer to: Shanley JD, Cline MJ: Phagocytosis of hematopoietic cells by blast cells in blast crisis of chronic myelocytic leukemia. West J Med 126:139-141, Feb 1977

Phagocytosis of Hematopoietic Cells by Blast Cells in Blast Crisis of Chronic Myelocytic Leukemia

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PHAGOCYTOSIS of formed bone marrow elements by neoplastic cells is generally associated with monocytic-histiocytic disorders,[1-6] although it has been described as a rare event in other neoplastic conditions.[7-9] We recently saw a patient with Philadelphia-chromosome-positive chronic myelocytic leukemia in whom there was striking phagocytosis of cellular elements during blast crisis.

Report of a Case

A 23-year-old Vietnamese woman was in good health until December 1974 when she noted the onset of mild fatigue, easy bruising and mild sternal tenderness. In February 1975 a routine blood count showed anemia and a leukocyte count of 104,000 per microliter (μl) with all developmental stages of the granulocytic series present on peripheral blood smear. Evaluation at that time showed an undetectable leukocyte alkaline phosphatase, a normal liver-spleen scan, and a bone marrow aspirate and peripheral blood smear consistent with chronic myelocytic leukemia.

Busulfan therapy was carried out for three weeks, and by May 1975 the blood counts had returned to within normal limits. However, in September the leukocyte count again began to rise, and the patient was referred to the University of California Medical Center at Los Angeles.

On initial evaluation the patient complained of frequent bifrontal headaches and occasional fever, but was otherwise asymptomatic. Findings on physical examination were unremarkable. Laboratory studies showed the following values: hematocrit reading, 39 percent; leukocyte count, 21,000 per μl; platelets, 400,000 per μl; leukocyte alkaline phosphatase, 28 (normal, 50 to 150). Values for serum electrolytes, glucose and creatinine, and findings on roentgenogram of the chest were all normal. Stool specimens were negative for ova and parasites. Skin tests for coccidioidomycosis and with tuberculin were negative, but mumps skin test was positive. Karyotype analysis of the bone marrow showed cells with 46 chromosomes and a single Philadelphia chromosome.

The patient left the hospital and therapy was resumed with busulfan, 2 mg per day, and allopurinol, 300 mg per day. During the next three weeks she noticed increasing headaches, the development of scalp tenderness and temperatures of 102°F (38.9°C). In addition, hepatosplenomegaly developed. Leukocyte count increased to 53,000 per μl with an increasing number of blast forms present on blood smear. In early November 1975 she reentered the hospital for evaluation of fever, headache and failure to respond to chemotherapy. Findings on cerebrospinal fluid analysis, computerized cerebral tomography, sinus and skull films, upper gastrointestinal series, abdominal ultrasound and mammogram studies were within normal limits. Urine and serum muramidase, and urine vanillylmandelic acid were also normal. Bone marrow examination showed a pattern consistent with the accelerated phase of chronic myelocytic leukemia with scattered nests of myeloblasts. Numerous large immature cells with basophilic cytoplasm, homogeneous nuclear chromatin, nucleoli and phagocytized intact cellular elements were present (see Figures 1 through 3). These primitive cells did not stain for peroxidase or for alpha naphthyl butyrase, a marker for mononuclear phagocytes.

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Submitted February 20, 1976.

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Karyotyping of the bone marrow at this time showed three abnormal cell populations. One showed 46 chromosomes with the XX pattern and one Philadelphia chromosome. One possessed 48 chromosomes with two Philadelphia chromosomes and an acrocentric marker. The last contained 49 chromosomes with the same pattern as the population with 48, but contained an additional C-group chromosome.

Evaluation of the patient's headache and fever, and an extensive search for a possible second neoplasm were negative. She was treated for two weeks with high-dose busulfan without improvement. Therapy was then changed to 6-mercaptopurine, 150 mg per day, but the development of pancytopenia during the subsequent three weeks limited further treatment. Repeat bone marrow aspiration and biopsy study at this time showed a highly cellular marrow of predominantly immature cells. Most myeloid cells were either blast cells or promyelocytes, and numerous blast cells contained ingested erythrocytes.

In December 1975 therapy with vincristine, 1.8 mg per week, and prednisone, 60 mg per day, was initiated, but produced no beneficial effect during a three-week course. During this period, blast cells containing ingested erythrocytes were observed in the peripheral blood smear. The patient remained pancytopenic and required both antibiotics and multiple transfusions of platelets and red blood cells. In early January blood loss into the subarachnoid space occurred and the patient died from subsequent respiratory arrest. An autopsy was not done.

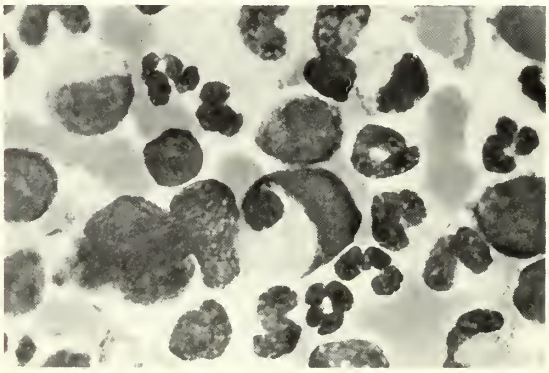

Figure 1.—An acidophilic normoblast engulfed by a blast cell in the bone marrow.

Discussion

A striking and unusual feature of this case of Philadelphia-chromosome-positive chronic myelocytic leukemia was the intense phagocytosis of blood cells that developed during blast crisis. Phagocytosis of various marrow elements by neoplastic cells was seen repeatedly in bone marrow aspirates, and erythrophagocytosis was present in peripheral blood smears. The phagocytic cells were morphologically primitive cells with prominent nucleoli and without granulation. They failed to stain for either alpha naphthyl butyrase (lipase) or peroxidase. Urine and serum muramidase were within the normal range. Using light microscopy and histochemistry it was not possible to determine the line of origin of these blast cells.

Phagocytosis is a well-recognized function of the granulocytic and mononuclear phagocytic cell series. In general, this capacity is associated with increasing maturation of granulocytes,[10,11] although myelocytes[10] and even myeloblasts[12] have been observed to ingest microorganisms or particles. However, immature granulocytes perform this function poorly. No reports of ingestion of cellular elements by granulocytes could be found in a search of the literature.

Phagocytosis of cellular elements is a characteristic feature of the monocytic-histiocytic disorders,[1-6] although it has been reported to occur

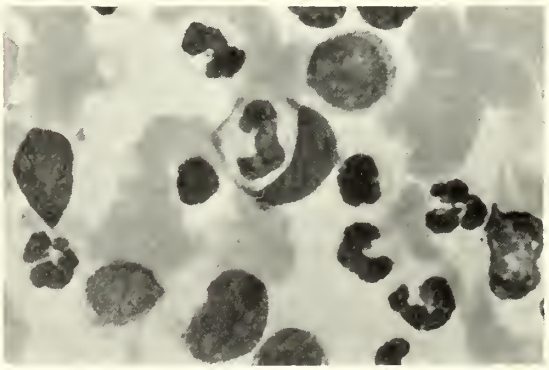

Figure 2.—A phagocytized neutrophilic band cell within a blast cell.

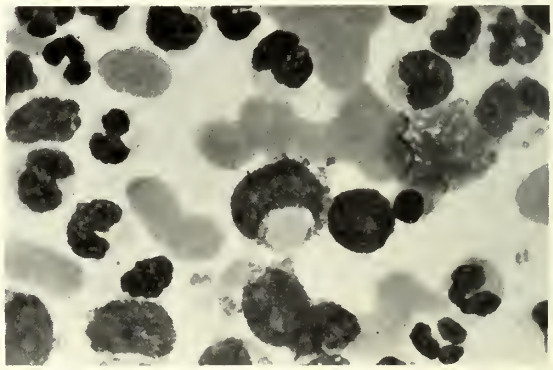

Figure 3.—An erythrocyte ingested by a leukemic cell in the bone marrow.

occasionally in normal bone marrow[13] and in hemolytic anemia.[14,15] Active phagocytic activity in mononuclear leukemia is well described.[1,3,16] Phagocytosis of cellular elements is common in histiocytic medullary reticulosis[1-6] and may be an occasional feature of histiocytic lymphoma. Other sporadic instances of phagocytosis of cellular components have been reported. Three cases of erythrophagocytosis in plasma cell leukemia have been described.[7,8] Two cases of red cell ingestion by carcinoma infiltrating the bone marrow have been reported.[9] However, no cases of this form of phagocytic activity in chronic myelocytic leukemia were found.

It is interesting to speculate on the significance of the development of phagocytosis during the evolution of chronic myelocytic leukemia. Current evidence suggests that chronic myelocytic leukemia is a clonal disorder of a pluripotential hematopoietic stem cell[17] since the Philadelphia chromosome marker can be found not only in polymorphonuclear leukocytes but also in precursors of red cells, eosinophils and platelets.[17-19] The disorder may involve mononuclear phagocytes as well, given the close relation between the developing granulocytic and monocytic series.[20] Phagocytosis may be a feature of very primitive mononuclear phagocytes[1,21] and may account for the striking ingestion of hematopoietic elements observed in this case.

Summary

In a patient with Philadelphia-chromosome-positive chronic myelocytic leukemia in blast crisis there was intense phagocytosis of formed blood elements by undifferentiated blast cells. Primitive cells containing ingested leukocytes, erythrocytes and platelets were seen in both the bone marrow and the peripheral blood. The possible implications of this unusual finding during blast crisis in chronic myelocytic leukemia are discussed.

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Fatal Ingestion of Table Salt by an Adult

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In 1963 sodium chloride poisoning was well publicized after the tragic deaths of six infants fed formulas inadvertently prepared with table salt instead of sugar.[1] Nonfatal salt poisoning has been described in a set of 14-month-old twins who consumed some from a box of commercial salt.[2] Fatal salt poisoning due to gastric lavage with hypertonic salt has been described in a 2-year-old and a 22-month-old child.[3] Moreover, the danger of using salt as an emetic both in children and in adults has been underscored by reported fatali-

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ties.[4-7] So, too, hypertonic enemas have led to systemic hypernatremia.[8]

We report here an unusual case of fatal salt ingestion.

Report of a Case

The patient was a 45-year-old woman with the clinical features of Prader-Willi syndrome; short stature (155 cm), obesity (86 kg), small hands and feet, mental retardation (IQ 75), consistent polyphagia and a diabetic glucose tolerance curve. In addition, she was receiving reserpine (Serpasil®), 0.25 mg three times a day, for hypertension. Otherwise her physical health was unremarkable; she received no specific antidiabetic therapy.

At breakfast, on the day of her death, it was estimated the patient ate four cups of jam supplemented with three to four heaping tablespoons of salt—conceivably under the impression it was sugar. Within two to three hours she became acutely ill. Admitted immediately to a local hospital, the salt ingestion was neither known to her nor suspected by the medical staff.

On examination the patient was noted to be massively obese and in a comatose state. Temperature was normal, pulse was 120 and respirations were 36 and labored. Blood pressure was unattainable, in part at least because of obesity. The lips and fingertips were cyanotic. Pupils were equal in size and responded to light. Neck veins were not distended. Chest was clear to auscultation. On cardiovascular examination a normal sinus rhythm and slight tachycardia were found; no murmurs were heard. The liver was not palpable. On neurologic examination there was response only to deep pain; plantar reflexes were bilaterally flexor; deep tendon reflexes were depressed.

Admission laboratory data for specimens of blood drawn before intravenous therapy was begun became available a little over an hour after admission and showed the following values: sodium, 190 mEq per liter; chloride, 166 mEq per liter; potassium, 3.8 mEq per liter; carbon dioxide, 15 mEq per liter; glucose, 582 mg per 100 ml; blood urea nitrogen, 15 mg per 100 ml; hematocrit reading, 47 percent; leukocyte count, 13,150 per cu mm, with 57 percent neutrophils and 43 percent band forms.

The hospital course lasted two hours. Initially the cyanosis responded to oxygen. Electrocardiograms showed a drop in the pulse from 120 to 70, with a progressive prolongation of the P-R interval from 0.20 to 0.24 seconds. The T waves became peaked. An hour and a half after admission, arrhythmias developed with ectopic QRS complexes. At that time the patient was anuric and 2 ml of meralluride (Mercuhydrin®) was given intramuscularly.

The patient was then transferred to another hospital 45 minutes away. There cardiopulmonary arrest occurred on arrival at the emergency room. On examination the pupils were dilated and nonreactive, and no activity was seen on an electrocardiogram. Cardiopulmonary resuscitation was unsuccessful and the patient was pronounced dead approximately six to seven hours after ingesting table salt and jam.

On autopsy diffuse subarachnoid hemorrhage, transmural necrosis of the stomach, gastric dilation, epithelial cell swelling of renal tubules, biventricular cardiac dilation and generalized passive vascular congestion of the lungs, liver and kidneys were noted.

Discussion

In previous instances of fatalities due to acute overdose of salt, a surprisingly small amount of sodium chloride has been involved. As Loeb notes, sodium's distribution within the body is largely confined to the extracellular fluids.[9] Assuming the proverbial 70 kg person whose extracellular compartment amounts to approximately 15 liters and assuming any ingested salt is rapidly and completely absorbed and distributed extracellularly before significant excretion can transpire, two teaspoons of salt (9± grams of salt or 150 mEq of Na^+) would result in an elevation of serum sodium concentration of 10 mEq per liter. Two tablespoons (30± grams) would lead to a 30 mEq increase—again assuming all of the above. Therefore, as noted previously[2] remarkably little "plain salt" proves patently toxic. If distribution throughout the extracellular compartment were to be delayed, severe hypernatremia would ensue with even smaller amounts. In this instance, best estimates are that a total of 45 to 60 grams of table salt were ingested—well in excess of the amount postulated to lead to significant hypernatremia.

It is well known that an absolute increase in the sodium chloride concentration in the extracellular space will increase the effective osmolarity, which will, in turn, promote a shift of water from the intracellular space. The extracellular ex-

pansion will continue until the two compartments are isosmotic. In this case report the patient ingested, in addition to the salt, a large amount of jam, which resulted in another osmotically active solute in the extracellular space. Using the formula summarized by Loeb, we calculated that the serum osmolarity reached 414 mOsm per liter as opposed to the normal 285 to 295 mOsm per liter with the salt contributing approximately 84 percent of the elevation, the sugar 16 percent.[9] Therefore, a greater shift of water from the intracellular space to the extracellular space could be expected due to the salt plus the glucose than from just the salt alone. The role of the glucose ingestion in this particular patient was probably more significant since carbohydrate metabolism is known to be altered in the Prader-Willi syndrome. The rapid shift of water from the cells to the extracellular space produces "shrunken" cells and an expanded vascular space. In the brain, this leads to distended cerebral vessels and subarachnoid, subdural and intravascular hemorrhage. Evidence of passive congestion may also be seen in the lungs and kidneys.[10] Acidosis has been described in hypertonic states and is ascribed to the shift of free hydrogen ions to the extracellular space.[11]

Acute salt poisoning has occurred under various circumstances including eating salt directly.[2] This report is unique in that a woman, because of her condition (Prader-Willi syndrome) and not age, ate a large amount of table salt with jam. The insatiable appetite and mental retardation commonly present in the Prader-Willi syndrome were the major contributory factors responsible for the ingestion.[12,13]

It is worth noting that there is no record of this patient's having vomited after the ingestion of the table salt. This supports the efforts of other authors to condemn the use of salt water as an emetic to treat acute poisoning.[2,4,5,7] To emphasize this point, it should be noted that within the year, five additional deaths consequent to the use of saline as an emetic have been reported; in one patient the serum sodium level was recorded at 227 mEq per liter.[14-16] Recommendations for the use of saline emetics must be expunged from first aid manuals.

Summary

A 45-year-old woman with Prader-Willi syndrome ate an excessive amount of jam and table salt. She became comatose and died within six to seven hours of the ingestion. Laboratory data confirmed hypernatremia, hyperchloremia, hyperglycemia, hyperosmolarity and acidosis. Once again this ubiquitous substance is documented as having lethal potentials. Its possible use as an emetic agent is decried.

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Refer to: Boyer TD, Sun N, Reynolds TB: Allopurinol-hypersensitivity vasculitis and liver damage. West J Med 126:143-147, Feb 1977

Allopurinol-Hypersensitivity Vasculitis and Liver Damage

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ALLOPURINOL is a xanthine oxidase inhibitor and is used in the treatment of hypercuricemia. The drug is well tolerated, with mild skin rash and gastrointestinal upset being the most common side effects.[1-3] Rare occurrences of alopecia,[4] agranulocytosis,[5] xanthine stones,[6] granulomatous

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hepatitis[7] and toxic epidermal necrolysis[8] have been reported. We describe three patients with severe reactions to allopurinol that included hepatocellular necrosis, hepatic granulomata, renal failure and exfoliative dermatitis secondary to a hypersensitivity vasculitis. A subsequent controlled challenge to allopurinol in one patient elicited a positive response. Since most hepatic reactions that occur during therapeutic drug usage are not accompanied by renal failure, the significance of a history of allopurinol ingestion may not be appreciated in patients like those described below.

Reports of Cases

CASE 1. A 29-year-old black man, a security guard, had been followed at Los Angeles County-University of Southern California Medical Center (LAC-USCMC) since 1973 for exogenous obesity, idiopathic hypoventilation and cardiomyopathy. Medications taken since 1973 were digoxin, furosemide and chloral hydrate. The patient was readmitted to LAC-USCMC in August, 1974 for difficulty in breathing felt to be secondary to a viral pneumonitis. A uric acid level of 14 mg per 100 ml prompted the use of allopurinol, 100 mg three times per day, beginning on August 28. He was then transferred to another hospital for long-term weight reduction and convalescence. Administration of the furosemide, digoxin and allopurinol was continued.

He did well until September 29 when a temperature of 103°F (39.4°C) developed. The fever was followed by deteriorating hepatic and renal tests, as listed in Table 1. Generalized pruritus was first noted on October 3 and the patient was transferred back to LAC-USCMC on October 4.

On readmission the patient was febrile to 102°F (38.8°C) and obtunded. An erythematous scaling rash was present on his face. He was icteric but the liver could not be palpated. Urine output was maintained at 1,000 to 1,200 ml per day. Findings on analysis of urine included 2+ protein, 5 to 8 leukocytes, occasional red blood cells, and numerous hyaline and granular casts. Mild leukocytosis (12,000 cu mm) without eosinophilia was present. The prothrombin time, initially 30 percent, rose to 89 percent following an intramuscular injection of vitamin K.

A liver biopsy was done on October 8. The hepatocytes were swollen and there was moderate hepatocellular necrosis, more pronounced centrally (Figure 1). Kupffer cell hyperplasia was present and the portal areas were widened with a mixed inflammatory cell infiltrate with a few eosinophils.

TABLE 1.—*Laboratory Values in Three Cases of Allopurinol Hypersensitivity*

Date	*Creatinine mg/100ml*	*SGOT†/SGPT‡*	*Serum Bilirubin§ mg/100ml*	*Alkaline Phosphatase¶*	*Albumin/Globulin gm/100ml*
Patient Number 1					
8/21/74	1.3	30/15	1.4/0.2	2.2	2.8/4.3
*8/28					
10/5	2.4	1300/940	14.4/11.9	4.0	2.7/5.0
10/16	5.7	1020/623	52.0/30.0	3.4	3.7/4.2
10/31	1.2	68/87	4.8/2.4	..	....
2/13/75	0.9	20/5	0.6/0.1	..	4.1/4.5
Patient Number 2					
*5/18/73	1.7	28/24	0.4/0.1	2.0	3.5/3.9
6/23	3.5	135/165	1.8/0.9	7.5	3.7/4.4
6/26	7.0	128/93	1.8/0.9	3.5	2.3/3.0
6/30	6.7	....	....	..	....
7/5	7.8	53/31	....	..	....
7/11	9.1	49/35	....	..	....
Patient Number 3					
8/12/74	1.7	35/30	0.4/0.2	2.4	3.3/7.0
*1/4/75					
2/14	11.3	40/35	3.1/1.6	6.3	2.4/3.5
2/21	8.4	....	....	..	....
2/24	5.7	110/150	2.8/1.2	8.5	3.0/4.0
3/16	2.0	35/60	1.0/0.4	3.4	3.2/3.9
5/12	1.5	35/12	0.3/0.1	1.6	3.4/3.9

*Date allopurinol begun.
†Serum glutamic oxaloacetic transaminase (5-40 units).
‡Serum glutamic pyruvic transaminase (5-35 units).
§Total/direct.
¶Bessy Lowry units (1-3).

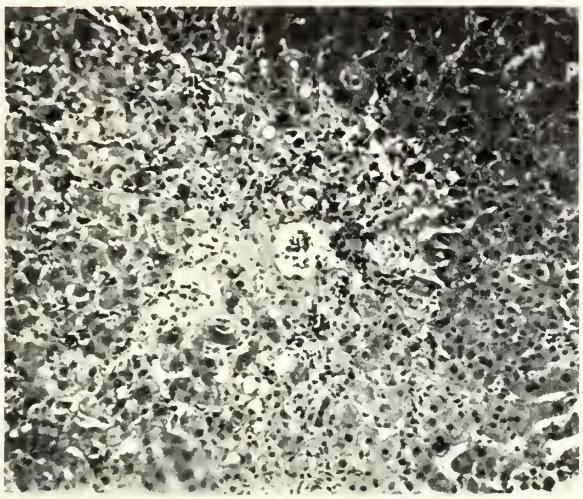

Figure 1.—Needle liver biopsy specimen in case 1 showing centrilobular necrosis with numerous acidophilic bodies. Paraffin section with hematoxylin and eosin stain; reduced from original magnification ×140.

Despite discontinuation of all medications the skin, hepatic and renal lesions progressed and therefore administration of prednisone, 60 mg per day, was begun on October 16. Concomitant with the use of prednisone, findings on the hepatic and renal tests showed improvement and the skin rash resolved. Administration of prednisone was discontinued after one month without a relapse of the clinical illness.

The patient was readmitted to hospital in February 1975 for a controlled challenge with allopurinol. He was taking no medications and results of repeat hepatic and renal tests were within normal limits. After obtaining informed consent, 100 mg of allopurinol was given orally. Three hours later generalized pruritus and a temperature of 102°F (38.8°C) developed. The fever subsided within 24 hours, but a mild exfoliating dermatitis developed four days later. The rash cleared in one week without treatment. Results of serial hepatic and renal function tests were within normal limits, with the only laboratory abnormality being a leukocytosis without eosinophilia.

CASE 2. A 59-year-old man was first admitted to LAC-USCMC in May 1973 because of syncope. He was known to be diabetic and taking insulin and also took hydrochlorothiazide for mild hypertension. The syncopal episode was thought to be secondary to an idiopathic seizure disorder and administration of diphenylhydantoin, 300 mg per day, was begun. Mild heart failure was treated with digoxin, and because of an elevated serum uric acid (10.8 mg per 100 ml), administration of allopurinol, 100 mg twice a day, was started on May 18. The patient was discharged on May 30 taking insulin, digoxin, diphenylhydantoin and allopurinol.

He returned to LAC-USCMC on June 23 with a seven-day history of fever and a two-day history of generalized pruritus. Ampicillin had been prescribed three to four days before admission to hospital. He was febrile to 102°F (38.8°C) and a generalized macropapular skin eruption was present. Findings on physical examination were otherwise unremarkable. No further ampicillin was given but there was continued administration of allopurinol, diphenylhydantoin and digoxin.

Results of the initial and subsequent laboratory tests are listed in Table 1. The leukocyte count was 5,800 to 7,500 per cu mm with 2 to 8 percent eosinophils. Urine output initially was greater than 1,000 ml per 24 hours; however, toward the end of his hospital course it fell to less than 500 ml a day. Analysis of urine consistently showed 1+ to 2+ proteinuria with occasional red blood cells but no casts.

Fever persisted and the skin rash worsened, with exfoliation. Administration of allopurinol was discontinued on July 2 and the diphenylhydantoin was stopped on July 9. A peritoneal dialysis was done on July 8 and hydrocortisone therapy begun on July 10. The patient died suddenly on July 12 with no preceding change in clinical status.

At the time of autopsy a generalized, bullous, exfoliative dermatitis was present, involving the skin, external genitalia and oral mucosa. Microscopically skin changes were noted that were consistent with toxic epidermal necrolysis. Disseminated intravascular thrombi with and without vasculitis were seen in numerous organs. A systemic vasculitis, characterized by fibrinoid necrosis, perivascular round cell infiltration, subintimal proliferation, sclerosis and hyalinization of capillaries, arterioles, small arteries and venules, was present in the breast, pancreas, liver, kidneys, prostate, testes, spleen and adrenals (Figure 2). Segmental glomerulonephritis was also present; the liver showed minimal pathology.

CASE 3. 67-year-old black man was followed at LAC-USCMC since 1964 for adult onset diabetes mellitus, mild hypertension, organic heart disease and glaucoma. He had received hydrochlorothiazide, digoxin, potassium chloride and alpha-methyldopa for several years. Administration of allopurinol, 300 mg a day, was begun on January

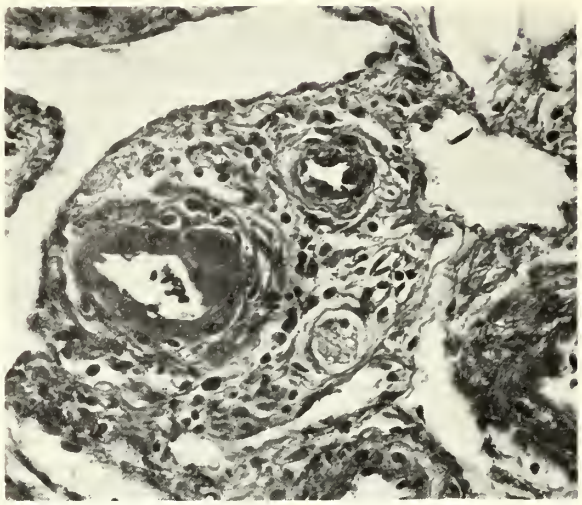

Figure 2.—Section from case 2 with arterioles in the periadrenal fat showing fibrinoid necrosis and perivascular inflammatory cell infiltration. Paraffin section with hematoxylin and eosin stain; reduced from original magnification ×350.

4, 1975 by his private physician. He presented at LAC-USCMC on February 3 with a three-day history of fever and deteriorating mental status. On admission, body temperature was 100°F (37.7°C). He was slightly obtunded; the liver was palpable 2 cm below the right costal margin and there was an erythematous scaling rash on his face. Administration of all medications, including allopurinol, was discontinued on admission. Analysis of urine showed 1+ to 2+ albuminuria, occasional leukocytes, and red blood cells and a few granular casts. Neutropenia developed, with the maximum depression occurring on the 11th hospital day (absolute neutrophil count 513 per cu mm). By the 14th hospital day the neutropenia had spontaneously resolved. Eosinophilia was never present.

A liver biopsy was carried out on the third hospital day. The portal tracts were widened by increase in connective tissue and infiltration by round cells and polymorphonuclear leukocytes. Epithelioid granulomata were present in the periportal areas.

The patient's initial hospital course was marked by fever, decreasing renal function and oliguria. Numerous antibiotics were given during his stay in hospital for possible sepsis; however, several blood and urine cultures revealed no growth. One peritoneal dialysis was done on the 11th hospital day. Administration of prednisone, 60 mg a day, was begun on the 15th hospital day, and coincided with a return of his temperature to normal. Two days after beginning administration of prednisone the urine output began increasing, renal function improved and the skin rash disappeared. In early May 1975 the prednisone was withdrawn without relapse.

Discussion

Nine cases of hypersensitivity reaction to allopurinol similar to the current three cases have been reported.[9-12] All of the salient clinical features are present in our three cases. The onset of illness was about four weeks after institution of therapy with allopurinol and it began with fever and pruritus or dermatitis—or both. Exfoliating dermatitis and renal failure became the dominant clinical features. Liver disease, although always present, was more variable in its severity. Eosinophilia was present in eight of the nine previously described cases but was seen in only one (case 2) of our patients.[9-12] The skin and renal disease progressed despite discontinuation of allopurinol administration and no improvement occurred until steroid therapy was instituted. The dermatitis and renal failure are secondary to a systemic vasculitis and segmental glomerulonephritis.[9,10,12] The hepatic lesion is not consistent and has varied from mild portal inflammation to centrilobular necrosis.[11,12]

In the cases being described and in the previously reported cases most patients were taking several drugs, making it difficult to establish a cause and effect relationship with allopurinol. The frequent use of thiazide diuretics in these patients (six out of nine) has led one author to suggest that they may contribute to the development of the allergic reaction.[12] The proven sensitivity to allopurinol in case 1 shows that allopurinol alone can cause two (fever and skin rash) and probably all of the features seen in the above cases. The failure to detect any abnormalities in hepatic and renal tests after challenge with allopurinol probably reflects the brief exposure to the drug, as in one reported case an inadvertent two-day challenge in an acutely ill patient resulted in worsening of his renal function.[11]

The acquired hypersensitivity in these patients could be directed against a metabolic product of allopurinol. Allopurinol has a half-life of only two hours while its major metabolic product, oxipurinol, has a half-life of 18 to 36 hours due to renal tubular reabsorption.[13] The immunologic role of allopurinol in the development of the vasculitis and glomerulitis has received limited

study. Gammaglobulin and complement have been found in glomeruli[10] and no lymphocyte transformation occurred upon exposure to allopurinol in the one patient studied.[12]

Allopurinol should be included with other drugs capable of causing hepatocellular necrosis and renal failure. It is unique in that the liver leison can be similar to that caused by carbon tetrachloride, methoxyfluorane and acetaminophen, but the renal lesion is glomerular instead of the tubular necrosis seen with the other drugs. The variable character of the liver lesion suggests that it is not secondary to the systemic vasculitis and may be a separate immunologic reaction to the allopurinol.

Allopurinol is a safe and useful drug with few side effects. It may, however, cause a severe hypersensitivity vasculitis that can be fatal. In a patient in whom a skin rash or unexplained fever, or both, develops when this drug is being given, hepatic and renal tests should be done. In the patient in whom the vasculitis develops corticosteroid therapy appears to be efficacious.

Summary

Fever, skin rash, renal failure and liver disease developed in three patients three to four weeks after treatment with allopurinol was begun. Two of the patients recovered following therapy with corticosteroids. After recovery from the initial illness, allopurinol was readministered to one patient and fever and skin rash recurred. Allopurinol hypersensitivity should be included in the differential diagnosis of hepatocellular necrosis and renal failure. Early diagnosis is essential because the continued administration of allopurinol may result in a protracted illness and increased mortality.

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Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgment before publication.

National Health Insurance and the AMA House of Delegates

To the Editor: Like a huge, unstoppable glacier, National Health Insurance (NHI) is grinding down upon us. That was the uncomfortable consensus of the House of Delegates of the American Medical Association at the recent meeting in Philadelphia.

It was not a decision easily arrived at. Only after many hours of hearings in the reference committee, and much heated oratory and parliamentary maneuvering on the floor of the House, were the delegates able to vote favorably on a positive AMA program.

The bone of contention? HR 6222. This is the bill the Board of Trustees hope to present to the Congress as a positive AMA approach to the problem of NHI. It is a compromise. It recommends catastrophic coverage, comprehensive health care insurance, a program that is compulsory for the employer but voluntary for the employee. It would build on the present private insurance industry and on our existing pluralistic health care system.

Delegates from Louisiana, Oklahoma and California, among others, fought tooth and nail, and often with eloquence and passion, against *any* legislation leading to NHI. The proponents, on the other hand, pleaded for acceptance of this compromise measure, asserting that to do less would be to go back to our old negative, reactionary stance. Moreover, they argued, the legislators who are the friends of medicine are begging us for some sort of a bill to use against those who would give us far less favorable legislation should we take a negative, uncooperative stand.

"What's wrong with negative actions?" asked an opponent who had obviously done his homework. "Out of the Ten Commandments there are seven negative ones. There are 52 negatives in the Constitution of the United States." Furthermore, the opposition contended that no matter what kind of a bill you give them, Congress will only use it as a base on which to build a far more comprehensive, socialistic program.

So it went, a seesaw battle. It seemed evident that the delegates individually wanted no more government medicine. But collectively they were resigned to following the more pragmatic, realistic course.

In the end, after the votes in favor of HR 6222 had been counted, there was no elation. More than one delegate headed home with the hope in his heart that somehow the NHI glacier might be slowed or stopped by the increased fear of a mountainous national debt, and that the specter of Britian's near-bankruptcy might bring a new awakening of legislative conscience.

Yet, who knows—will that glacier only move faster down through that warm and sunny Carter valley?

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A Munchausen Alert

To the Editor: Two recent letters to the *Annals of Internal Medicine* have described a patient who was felt to be a bonafide example of Munchausen syndrome.[1,2] This now famous patient was recently in our facility and provided an unforgettable experience.

In mid-December a 44-year-old white man was admitted to the surgery service of the Sacramento Medical Center for evaluation of swelling in his left hand. Since he admitted to being an abuser of parenterally given meperidine hydrochloride (Demerol®), it was felt that an infection had to be ruled out. He claimed that he had chronic leu-

kemia, and indeed his leukocyte count was 31,000. He made other statements that had an air of incredibility; for instance, he said he had contracted filariasis while traveling around the world. During his stay in the hospital he acted strangely, prompting his ward doctor to request a psychiatric consult. He had the audacity to order Demerol injections for himself by phoning the nurses' station from his room telephone and impersonating his ward physician. When warned that his supply of Demerol might be cut off, he signed out of the hospital against medical advice and exited in an ambulance which he himself ordered. Since he reported that his leukemia had been diagnosed in a California Veterans Administration hospital, an attempt was made to confirm this by telephone, but we gave up this effort after five successive VA hospitals across the country replied that his records had been forwarded to another facility.

The patient stated that he had come to Sacramento because some of his relatives lived there. A phone call to the patient's father verified this claim. Furthermore, when asked where the patient maintained permanent residence, the father answered that his son did not have a home base but spent most of his life in hospitals.

This patient fits the description of the wandering patient with Munchausen syndrome with leukocytosis mentioned by the references above. Both letters are from East Coast hospitals, but it appears that the odyssey of this man has recently taken him to the West Coast. During his stay in hospital here many superfluous procedures and evaluations were carried out. This man, like any patient, deserves an objective appraisal of his medical problems wherever he travels; however, it would seem beneficial to the hospitals in which this patient gets admitted to recognize his psychiatric problem so that needless tests and examinations are not done. Moreover since he has a propensity to impersonate physicians, the nursing staff on his ward should be advised to accept only written orders for his medications. The purpose of this letter is thus to alert West Coast physicians of this patient's arrival and to predict frequent visits by him to his home state of California where his relatives reside.

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More on Physician's Assistants

To the Editor: In the December 1976 edition of the Western Journal was a letter to the editor written by Dr. Frank Z. Reade, concerning physician's assistants [West J Med 125:498, Dec 1976].

I must take issue with Dr. Reade and his interpretation of physician's assistants, and the mode of practice in the state of California, and particularly in the Fullerton area.

There are good doctors and bad doctors as we all know. There are also good and bad physician's assistants. To make a generality, which Dr. Reade has done because of one incident, to me seems very short-sighted. I would take pleasure in explaining to Dr. Reade the program that physician's assistants must complete to earn their degree at the University of Southern California. I have had the pleasure to be associated with the University of Southern California since their physician's assistant program was first started some four years ago. This program was started to assist physicians, and in no way was it designed to supplant physicians. If there is a doctor in this area who is having his physician's assistant call himself "doctor," a title he has not earned, this physician should be called on the carpet and should be reported to the Board of Medical Quality Assurance. The Board of Medical Quality Asurance not only issues licenses to practice medicine to physicians and surgeons, but also issues licenses to certified and qualified physician's assistants. We are under the same board and therefore subject to the same disciplinary actions.

The role of physician's assistants in the practice of medicine today will become more and more evident as time passes. Physicians in their busy practice need help in the routine examinations of patients and the screening of patients with acute illnesses. All of the physician's assistants with whom I have been in contact through the University of Southern California have been outstanding young men and exemplify their profession by passing the national boards for physician's assistants and becoming licensed by the state of California. This protocol is much the same for physician's assistants as for medical doctors. The state law states that a physician's assistant must

identify himself as a physician's assistant and not as a doctor; he must wear a name tag with his name and the description that he is a primary care physician's assistant. In addition, the doctor's office must have a sign to inform patients. All of these criteria must be met by the supervising medical doctor.

Dr. Reade's letter to the editor gives one man's opinion concerning one man's experience. It would be very helpful to Dr. Reade, as it would be to other physicians in the state of California if THE WESTERN JOURNAL OF MEDICINE would publish an article concerning physician's assistants in the state of California, where they are practicing and under what type of supervision.

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Nutrition in Medical Practice

TO THE EDITOR: In the Bicentennial Editorial Essay entitled "A Broader Knowledge Base for Medicine" it is pointed out that "There are many signs that rational scientific medicine, as it has developed so far, may be falling short of both public and professional expectations. . . . A physician must therefore not only have some knowledge of the person and of human behavior, but also some awareness of the characteristics of the environment and an understanding of the relationships of persons to their environments." [Watts MSM: A broader knowledge base for medicine (Bicentennial Editorial Essay). West J Med 125: 383-384, Nov 1976]

This leads us to consider the nutritional environment of our patients, and raises an important question: Do food selections supply the body cells with the proper amounts of all the nutrients they require for the maintenance of robust health? Also, do they supply proper amounts for recovery from disease or injury?

A careful diet history helps answer these questions and simplifies the application of nutrition in medical practice. Laboratory tests may be of some value, but a detailed diet history, while not perfect, helps detect and correct faulty food habits, and this improves the quality of life. For instance, in my practice, data from the diet histories of 300 adult patients selected at random showed that 73 percent had been selecting deficient diets.[1] Specific advice on the necessary corrections was then easily given and understood.

For a diet history, physicians can prepare and have printed a list of questions. A copy of these is given to each patient, who writes the answers while in the reception room. On the list should be questions regarding the intake of the four basic food groups:[2]

1. The Milk Group—milk, buttermilk, yogurt, cheese.
2. The Meat Group—meats, fish, fowl, dried beans, nuts, eggs.
3. Fruits and Vegetables—includes green and yellow vegetables and citrus fruits or tomatoes.
4. Breads and Cereals—rice, wheat, oats, rye (whole grain preferred).

Questions regarding the intake of milk, for example, may be put this way: Do you drink milk or buttermilk regularly? How many glasses per week? How many helpings of cheese per week? What about ice cream, and milk on cereals?

Physicians should learn which are the chief nutrients in the foods of each of the four groups. More questions can then be added to the diet history form to find whether a patient gets these nutrients. Physicians should also ask about the intake of "junk foods," sweets, pastries and soft drinks; as well as about the intake of alcoholic beverages. Does a patient, for instance, usually make a breakfast of sweet rolls and coffee?

The general plan for the diet history questionnaire is to add as many questions as seem desirable. The printed sheet takes none of a doctor's time, and the answers can be quickly recognized. If a patient is selecting a variety of foods from each of the four groups, the chances are that his diet is adequate. But if he is not eating foods that contain the main sources of, say, vitamin A or C, or calcium, it does not take long to draw his attention to these errors. It will be a rewarding experience for both the physician and the patient.

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Estrogen Therapy in Postmenopausal Women

To the Editor: I should like to take issue with Dr. Gilbert S. Gordan's somewhat hasty dismissal in the August 1976 issue of the notion that estrogen therapy in postmenopausal women causes uterine cancer.[1] In his otherwise excellent clinical discussion of postmenopausal osteoporosis at a University of California, San Francisco, Medical Staff Conference, Dr. Gordan presented two or three arguments that led him to the conclusion that "There is no evidence of increased mortality from endometrial carcinoma." Being deeply disturbed about the potentially dangerous effect this attitude may have in the clinical community, particularly in light of the relief expressed by clinicians exposed to his discussion,[2] I should like to try to refute Dr. Gordan's arguments, and to summarize briefly some of the abundant evidence supporting the notion that estrogens are carcinogens.

There are three recent and excellent epidemiologic case-control studies in women (only two of which Dr. Gordan cited) showing that estrogens increase the occurrence rate of endometrial carcinoma by a factor of between five and eight.[3-5] A risk factor of this magnitude is considerable; if all postmenopausal women were subject to such a risk, for example, the overall incidence rate of carcinoma of the corpus uteri would make it the commonest cancer in American women. There is recent survey evidence from the Seattle-Tacoma area that more than 50 percent of menopausal women have received replacement estrogens for at least three months, and that median duration of use is ten years.[6] United States Department of Commerce figures indicate nearly a quadrupling of dollars spent for these medications since 1963.[7]

Dr. Gordan has presented essentially three arguments: (1) That there has been no real increase in endometrial cancer (mortality); (2) That the three observed cases of endometrial cancer in his own case series of 220 estrogen-treated women did not differ significantly from the expected "one or two cases"; (3) That the elevated risk associated with estrogen therapy in recent epidemiologic studies is the result of increased case-finding, which is, in turn, the product of more frequent diagnostic curettages to which such women are subjected because of estrogen-induced bleeding.

Regarding the first argument, there is new and abundant evidence of a precipitous increase in endometrial cancer incidence in the past several years. Indeed, Cramer and co-workers[8] expressed perplexity that they did not find an increase when Third (1969-71) and Second (1947-49) National Cancer Survey rates were compared. This artifact is now largely ascribed to two sources: First, misclassification of cervix cancers whose locations were often described simply as "uterine" in the earlier survey to the corpus category.[9] Second, the large number of women (as many as 25 to 40 percent of the postmenopausal population) in whom surgical hysterectomy has been done in the interim period has effectively decreased the real population-at-risk, while rate calculations continue to use census figures in the denominators. This latter argument was suggested by Cramer and co-workers in this very paper.

Weiss and associates have shown in six population-based United States cancer registries for which each year's rates are available since 1970 or before, that in all six (Connecticut, Hawaii, New Mexico, Oregon, San Francisco Bay and Utah) the uterine cancer incidence rates have risen,[10] in all but one they have risen every single year; the annual rise has been astoundingly more than 10 percent. In the five-county San Francisco Bay Area, the 1969 rate was 24.9;* in 1973, 40.3. Analysis of age, race and histologic type shows that the increase is observed only among whites, is greatest in the age groups between 45 and 70, is accounted for almost entirely by adenocarcinoma, and is highest in suburban areas such as Marin County.[11] In Alameda County, incidence rates from 1960 through 1974 have risen in every five-year age-group from 45 to 85. Aggregate rates for white women aged 50 to 74 have risen from 72.6 to 184.9* in the 13-year period from 1961 through 1973.[12]

Analysis of data abstracted from Vital Statistics of the United States for the years 1968-1972 shows that mortality rates for cancer of the uterine corpus (ICDA 182.0) have risen each year during that period. However, death rate analysis is complicated by the rather large proportion of noncervical uterine tumor deaths relegated to the site-unspecified group (ICDA 182.9), a propor-

*New cases per 100,000 women per year.

tion larger than that belonging to the corpus category.

Gordan's own 220-woman series, with fewer than two expected cases, is not of adequate size to test the hypothesis. It would have helped the audience to know how the expected number was calculated, and using what statistical test and at what probability it was decided that the observed number of cases was not significant.

Dr. Gordan's major argument hinges on the notion that the real explanation for the recent epidemiologic evidence is the increase in case-finding resulting from diagnostic dilatation-and-currettages carried out because of estrogen-induced bleeding. He cites two papers in which the controls were bleeders and no estrogen-associated risk was demonstrable.[13,14] Neither of those studies was population based or carefully organized epidemiologically. Both took patients largely from a time-period before massive use of estrogens and so these women had little possibility of exposure to exogenous estrogens. Finally, the requirement that controls be bleeders necessitates inclusion in the control series of women with abnormal endometria of a variety of types. Such pathological entities may well be precancerous or estrogen-induced, or both. In either case, the controls would, under the estrogen-cancer hypothesis, have a falsely elevated proportion of estogen-exposed women.

If Gordan's theory of increased case-finding were correct, and the estrogen-cancer hypothesis is rejected, then one would be forced to conclude that among normal postmenopausal women there is a huge number of latent, subclinical or undiagnosed uterine cancers, perhaps five to eight times the number ordinarily being diagnosed, which would be found if they came to currettage. We know of no evidence that this is the case, and certainly the large numbers of uteri removed because of fibroids or other benign disease would provide adequate pathologic material for testing such a hypothesis. Furthermore, in one of the three recent epidemiologic studies, the controls were all women with other gynecologic neoplasms, including 206 of 317 with cervix cancer.[4] Undoubtedly, these controls' uteri were subjected to histologic examination in a sufficient number of instances that this study alone constitutes refutation of Dr. Gordan's hypothesis. Furthermore, the recent increases reported for endometrial cancer do not include disproportionate fractions of localized or *in situ* cancer. The proportions of *in situ,* localized, regional and disseminated tumors have not changed during the period of rapidly increasing estrogen use.[15]

In 1937 Allen, Smith and Gardner[16] showed there to be a huge increase in vaginal mucosa mitosis after a single injection of estrogens; such changes were also found in the uterus.[17] Both Beatson[18] and Loeb[19] have shown a dependency of breast cancer upon functioning ovary or ovarian hormonal stimulation.

A large number of clinical reports[20-27] pointed toward an increase in endometrial cancer among women previously treated with estrogens. In a host of laboratories, many lines of evidence accumulated showing a relationship between estrogen exposure and the occurrence of breast or genital cancer.[28-30] These reports showed that tumors could be reproduced repeatedly at eight organ sites in five different species of animals. Uterine mesotheliomas have been produced regularly in squirrel monkeys following estrogen administration.[31]

In humans, there are at least five reports connecting vaginal adenocarcinoma in young women to previous maternal exposure to estrogens.[32-36] The point has been made that these adenocarcinomas are histopathologically similar to those of both endometrium and ovary.[37] Furthermore, the age of these adolescent patients implicated estrogens as having about a 15-year latency period. This may mean that any currently detected increase in endometrial adenocarcinoma is merely the beginning; that we are still on the upswing of the curve, as far as time is concerned.

Therefore, I believe, the medical community must temper its awareness of the therapeutic and placebo effects of conjugated estrogens in postmenopausal disease with the understanding that there are numerous pieces of evidence supporting the hypothesis that estrogens are a serious and potent carcinogen or cancer promoter for endometrium and other tissues; that the risk of endometrial adenocarcinoma is probably five to eight times greater with use of these medications; that this would mean that a woman using such medicine at and after age 45 would have a risk of at least 500 in 100,000 of contracting this disease for every year of her life, or a cumulative risk of more than one in eight if she is expected to survive to age 75. While there are some reasons not to accept this conclusion, with such a heterogeneity of evidence and with such a serious and frequently lethal disease, I believe the burden of

proof now rests with those advocating use of these drugs for therapy of postmenopausal conditions. Until there can be presented more convincing evidence that estrogens are *not* carcinogenic, it is my clear and unequivocal conclusion that the clinical community should and must withhold such therapy from all but the most severely ill patients.

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Dr. Gordan Replies

To the Editor: Dr. Stephen Brown's thoughtful critique gives me the opportunity to expand my "somewhat hasty dismissal of the notion that estrogen therapy in postmenopausal women causes uterine cancer." I share Dr. Brown's concern. Certainly no physician takes any cancer lightly. The reader may judge whether I have dismissed this important matter hastily. If one accepts at face value, as Dr. Brown does, the reports of Ziel and Finkle* and Smith and co-workers,* and the subsequent report of Mack and co-workers,* one would have to decide whether the risks of endometrial cancer outweigh the established certainty of fractures of the vertebrae, wrists and hips with their attendant morbidity and mortality in estrogen-deficient ethnically predisposed women (postmenopausal or oophorectomized). It is not correct that endometrial cancer is highly lethal; the type of cancer associated with estrogen therapy is most likely to be detected early and at a curable stage, probably because of proper examination for uterine bleeding. In the study of Smith and associates, 95 percent of the estrogen-associated cancers were Stages 0 or 1 (atypical adenomatous hyperplasia or carcinoma *in situ)*—which would not be recorded as cancers in the San Francisco Bay area Cancer Registry.[1] Only one was associated with deep myometrial invasion. In contrast, 25 percent of the cancers not associated with estrogen were in the higher stages of

*References 3-5 above.

malignancy and more deeply invasive. It should be noted that mortality figures from the National Center for Health Statistics show a constant low mortality from this cause accounting for 1.4 percent of all cancers in women for the period 1968 through 1974.[2] There were 2,252 deaths from corpus cancer in the United States in 1974. A quarter of these in blacks were myometrial sarcomas. I know no evidence that hysterectomy increased in this period; the report of Bunker in 1970[3] suggests that the major increase preceded this period. Brown's interpretation of Cramer's data* is opposite that of Cramer himself who concludes that endometrial cancer mortality is declining.

I cannot agree that the three retrospective case-control studies prove that estrogens cause cancer. I consider all three erroneous and illogical for the following reasons:

- Not all the so-called "cancers" were cancers. Smith's 95 percent Stage 0 and 1 cases are cited above. Ziel's series was subsequently reviewed by three pathologists headed by Arthur Hertig.[4] Ziel had based his data on 94 "cancers" but only 66 were accepted by all three pathologists and 76 by two. As far as I can ascertain, Mack's cases have not been subjected to extramural review. The difficulties of differentiating estrogen-induced hyperplasia from early carcinoma are well known and have recently been reviewed in connection with the present problem by Kistner.[5]
- Many of the women (28 percent of Ziel's series) received estrogen only in the three-year period preceding diagnosis. Since endometrial cancer usually developed over many years,[6] how many of these women were given estrogen to regulate perimenopausal bleeding actually due to preexisting carcinoma?
- The "cases" and "controls" were not similarly examined. It is not surprising that women subjected to curettage have more endometrial abnormalities read as cancer than unexamined women.
- In Smith's study the "controls" were women with other gynecologic carcinomas, two thirds of them carcinoma of the cervix. Since this disease occurs most commonly in the most neglected socioeconomic class while carcinoma of the endometrium is most common in the affluent, it is not surprising that estrogen administration was less frequent in poor than in rich women.
- Ascertainment bias is probable, for example, in Ziel's study where only cases reported to the Tumor Registry were included. But not all cases were reported to the Registry. It is not surprising that women who see doctors more often and are therefore more likely to be reported to the registry receive estrogen more frequently than women who do not. Exclusions of hysterectomized controls undoubtedly lowers estimation of control incidence of estrogen therapy.
- The logic is bothersome: How can one apply random statistics to a subset of patients with particular socioeconomic and medical characteristics?
- Even if increased association is established it does not necessarily prove cause. Increased association could even be spurious. In a witty, heuristic presentation of this important epidemiologic consideration, the great statistician Jerzy Neyman describes a strong association between the ratio of storks to women in 54 counties in California and the birth rate.[7] This is clearly a spurious correlation; it does not prove that storks bring babies.

Weiss describes increased "incidence" of endometrial cancer in eight selected Cancer Registries. I put incidence in quotation marks since the number of women at risk is not known. The last census with such detailed information was taken in 1970. Subsequent migratory population shifts and public support for medical care undoubtedly have altered the population base, certainly in California. Similar increases in incidence of endometrial cancer are reported from Norway[8] where estrogen use is rare, and from Czechoslovakia[9] where estrogen use is reportedly nil. Obviously, increased detected incidence can result from extension of medical care to previously neglected population, from better investigation of uterine bleeding and from changing diagnostic criteria to increased borderline histologic changes —all of which have probably occurred in the United States in the past decade. The registries Weiss selected used widely varying diagnostic criteria: Connecticut includes *in situ and* noninvasive tumors; the San Francisco Bay area registry does not. Increased estrogen use is certainly not the cause of the increased incidence of endometrial cancer noted in Norway and Czechoslovakia.

I am sorry that Dr. Brown doesn't like the studies of Dunn and Bradbury† or Pacheo and Kempers;† Greenberg and I[10] consider them better

*Reference 8 above.

†References 13, 14 above.

controlled than the three he cites. Estrogen use was not uncommon at the time of these studies: 28 percent of these indigent women studied at the University of Iowa a decade ago had received estrogens. Dunn and Bradbury anticipated Dr. Brown's criticism by excluding women bleeding from hyperplastic endometria. In answer to Dr. Brown's question, the incidence of corpus cancer in both the Second and Third National Cancer Surveys peaked at the postmenopausal age of 62 and was constant at 80 per 100,000 women. My 220 estrogen-treated women averaged 62 years of age at the start of treatment and were treated for 1,868 patient years. Random incidence therefore would have produced $\frac{80}{100,000} \times 1,868 = 1.5$ cases: "between 1 and 2 cases."

We detected three cases of carcinoma of the endometrium, all *in situ* and all found because of curettage for breakthrough bleeding. I do not claim that 220 cases are adequate for epidemiology of uncommon cancers. They sufficed for fracture incidence, the prime purpose of this study, since osteoporotic women average 50 to 70 fractures per 1,000 patient years.[11,12] My patients who received full replacement doses of estrogen sustained only three fractures per 1,000 patient years.[13]

Of course estrogens are carcinogens, at least when given continuously in large doses to susceptible strains. Estrogens are carcinogens in exactly the same sense that digitalis and vitamin D are lethal poisons. The young women with clear cell carcinoma of the vagina to whom Dr. Brown refers had been exposed to very large doses of nonsteroidal estrogens prenatally. The main thrust of my paper is that surprisingly small doses of estrogens which rarely produce endometrial hyperplasia or bleeding suffice to prevent postmenopausal bone loss. Very recent data[14,15] show that 20 to 25 μg per day of mestranol or 0.625 mg per day of conjugated estrogens are adequate for this purpose. Since postmenopausal bone loss, which leads to fractures of the vertebrae, wrists and hips in postmenopausal or oophorectomized women can be prevented, epidemiologists and other public health workers could help to stamp out preventable crippling and sometimes fatal fractures in ethnically predisposed women. We need accurate data on how many elderly women die of hip fractures, not presently recorded as a cause of death in vital statistics, and whether estrogen prophylaxis can prevent these fractures and deaths. Properly carried out retrospective studies have produced extremely important information, for example, 90 percent of the 90,000 lung cancer deaths this year will occur in smokers. Retrospective studies are notoriously difficult to control and have brought forth some associations which were subsequently refuted—for instance, reserpine and breast cancer, coffee and myocardial infarcts. Horwitz and Feinstein note that many retrospective studies fail to meet the criteria of common sense and logic.[16] It is a source of great concern and a potential hazard to American and international health that public policy has been based on such studies. Perhaps the one benefit of the present concern will be better examination of estrogen-treated women. In evaluating any therapy, it is essential to weigh risks versus benefits. But the current controversy is not simply a matter of trading off the risk of endometrial cancer for that of osteoporosis. In my carefully considered opinion, it is now established that the menopause or oophorectomy leads to bone loss. I do not believe it has been shown that properly administered estrogens cause cancer. A large number of prospective studies show that they do not.

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Refer to: Tait K, Winslow G: Beyond consent—The ethics of decision-making in emergency medicine (Trauma Rounds). West J Med 126:156-159, Feb 1977

Trauma Rounds

Chief Discussants
KAREN M. TAIT, BS
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Editors
DONALD D. TRUNKEY, MD
F. WILLIAM BLAISDELL, MD

This is one of a series of Conferences on Trauma at San Francisco General Hospital

Beyond Consent—The Ethics of Decision-Making in Emergency Medicine

EDITOR'S NOTE: Karen Tait is a third-year medical student at the University of California, San Francisco. Gerald Winslow is Assistant Professor of Religion at Walla Walla College, Walla Walla, Washington and a PhD candidate in Religion and Society at the Graduate Theological Union, Berkeley. These students participated in a summer fellowship program supervised by the Health Policy Program at the University of California, San Francisco. They had an eight-week rotation on the Trauma Service at San Francisco General Hospital with Dr. George F. Sheldon as their preceptor. Their impressions and analysis of the ethical and informed consent considerations of the emergency situation were felt applicable for Trauma Rounds. The authors wish to thank Michael Garland, PhD, and Albert Jonsen, PhD, for invaluable guidance and comments.

INCREASING ATTENTION is being given to the problems of informed consent in the practice of medicine.[1-3] Although obtaining informed consent for medical interventions is generally considered imperative, emergency medical care is a widely recognized exception. The ethicist Ramsey[4] defends the right of patients to consent to treatment but acknowledges that in medical emergencies assumed or implied consent is sufficient. Shartel and Plant[5] suggest that it is more appropriate to recognize that the law grants authority to act without reference to an injured person's consent, and that consideration of a "fictitious" consent adds unnecessary confusion. Recently, Johnson and Trimble[6] have discussed the problems encountered in treating a verbally abusive and unwilling patient in an emergency and concluded that physical restraint should be used when necessary and that thorough evaluation and treatment should be carried out regardless of the patient's consent. Only a few discussions[7,8] have attempted to resolve the many ambiguities of informed consent in an emergency, and these are largely from a legal point of view.

The purpose of the present study is to analyze the *ethical* issues related to the problems of consent and decision-making in emergency medicine. The authors observed emergency room practices on the trauma service of the San Francisco General Hospital for two months. Each of the authors was assigned to one of the two trauma teams at the hospital. Observations were made during numerous shifts, interviews conducted with staff members and rounds attended. Special attention was given to the decision-making process of the hospital's emergency room staff and the trauma service. Logs were kept and later analyzed in detail. The primary concern was for critical emergencies, such as trauma, myocardial infarction and drug overdose. Some of these patients were unconscious; others were conscious with varying levels of awareness. For simplicity, the word "emergency" is restricted to critical cases in which lives depended on immediate supportive treatment.

Emergency medicine is characterized by the need for rapid intervention, sometimes calling for aggressive measures at a time when pertinent in-

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formation is inaccessible and medical histories are sketchy. Moreover, if a patient is unconscious or irrational, or an inpenetrable language barrier exists, explaining the necessary medical procedures becomes impossible. Other patients at various levels of consciousness or apparent rationality, express the desire *not* to be treated in spite of manifestly serious conditions. This predicament is sometimes managed by having a close family member give "proxy" consent in order to satisfy legal requirements. But when the patient is unaccompanied by a family member, even proxy consent is impossible.

If a physician determines that a patient is incapable of making a rational decision, the medicolegal principle of "reasonable therapeutic restraint" may be appropriate. The courts have generally protected physicians who take whatever measures are deemed necessary in a medical emergency.[9] However, whether or not a physician acts, he *may* be legally liable. If he treats the patient without the patient's consent, the physician may be sued on the grounds of assault and battery. If, on the other hand, the physician does not restrain and treat the patient, he may be sued for negligence.[6]

Measures taken contrary to the patient's will require an accurate evaluation of the patient's mental status which, under emergency circumstances, is subject to a wide array of influences. Rational judgment may be affected by such conditions as cerebral hypoperfusion, central nervous system injury and drug intoxication. Psychological defense mechanisms such as denial and regression[10] may be used by injured patients and result in a failure to recognize the need for treatment or a childlike dependency on others.

Medical advances in resuscitation techniques, especially for trauma victims, have given impetus to aggressive treatment of most patients. For example, a 19-year-old-man was brought to the emergency room with a stab wound to the chest which penetrated the right ventricle of the heart. Upon arrival he was in severe shock and hypothermic (92°F). In earlier years it probably would have been considered impossible to save such a patient. However, aggressive resuscitative measures were initiated. In the trauma room, blood loss from the wound was reduced by thoracotomy before the patient was taken for emergency surgical operation. During several weeks in the intensive care unit, the man failed to respond to verbal stimuli, although his overall condition gradually improved. Eventually, he regained mental alertness and subsequently recovered to the extent that he was able to return to work.

In another case, extensive resources, including the services of a large proportion of the available personnel, were utilized in the treatment of a 34-year-old woman suffering from a severe upper gastrointestinal hemorrhage. In spite of all efforts at resuscitation, neurological evidence of brain death became apparent within 24 hours. Consent was obtained from the family to remove her kidneys for transplantation. Three days following admission the woman died. From the perspective of the medical staff this case did not represent an unmitigated failure. The family was reassured that the obligation to use all available means to save the patient's life was fulfilled and, moreover, the donation of the patient's two kidneys benefited two repicients.

The ethical approaches utilized by the medical personnel when making decisions in emergency situations seemed consistent with a predetermined decision to maintain life in virtually all emergency cases. Summarized as an operating principle, the prevalent attitude appeared to be: Always respond with whatever measures seem necessary in order to maintain (or resuscitate) vital functions whether with, without or against the patient's expressed will whenever urgent circumstances make attempts to obtain the patient's informed consent impractical.

In neither of the two cases just cited did the patients have the opportunity to consent to treatment. Presumably they would both have wanted all measures taken that might have been essential in attempting to preserve their lives. In recent years, however, this principle of preserving life whenever possible, sometimes called "vitalism," has come under attack. Fletcher argues that the "vitalistic ideas that life as such is sacrosanct, the highest good and somehow both sacred and untouchable, is obviously not tenable in actual practice."[11,12] McCormick[13] claims that quality-of-life decisions must be made; the vitalism which has characterized much of medical practice is a kind of "idolatry."

Along with criticism of the vitalistic approach, recent years have witnessed an expanding discussion of the patient's right to terminate or forego certain types of treatment—even essential life-saving treatment.[14] Commentaries on the well-known case of Karen Quinlan have indicated a similar concern.[15] Some patients have written

"living wills" which set the conditions and limits for life-saving intervention,[16] but a physician is more likely to encounter the desire to stop treatment as a verbal expression by the patient.

In commenting on a case in which a burned patient wished to terminate treatment, Engelhardt argues that the patient's decision must be honored, yet he also allows for the notion that *emergency* treatment might legitimately be forced on a patient in order to guarantee a later exercise of rational choice. ". . . One can justify treating a burned patient when first admitted even if that person protested: One might argue that the individual was not able to choose freely because of the pain and serious impact of the circumstances, and that by treating initially one gave the individual a reasonable chance to choose freely in the future."[17]

The making of decisions for another without regard for the involved person's will is often discussed under the heading of "paternalism."[18] Such a practice seems to run counter to the generally held principle of respecting the autonomy of individual persons. Paternalistic decisions are, however, frequently made. Many philosophers have recognized the limited but unmistakable legitimacy of this category of actions in certain situations. Children and even mentally competent adults are guarded against experiences and practices considered detrimental to their well-being, such as the use of street drugs.

It should also be recognized that even when a physician relinquishes the decision-making power, a kind of paternalistic judgment has been made. After initially assessing the patient's competence, the responsible physician provides or withholds the approval necessary to implement a patient's decision. For example, in the hospital studied, two patients under the same doctor's care wished to leave the hospital against medical advice on the same evening. Both patients were in need of observation, one for symptoms of suspected acute appendicitis and the other for complications of a drug overdose. The first man appeared to be rational and cooperative but preferred to watch for developing symptoms at home. The second patient showed his ineptitude during an attempt to get out of bed by upsetting his IV stand and breaking the bottle. The physician in charge released the first man with instructions to call at the first sign of problems but retained the second man against his wishes. Of course, in either case the patient could presumably undertake legal action to challenge the physician's judgment, but the potential for such action in the emergency setting is virtually nil. Furthermore, securing a court's judgment simply moves the power of paternalistic ratification from the physician to the court.

What is needed is a principle for action which respects the patient's autonomy and takes into account the need to make some paternalistic decisions for the patient. Philosopher John Rawls approaches the problem by asking his readers to imagine a scene in which a group of people have been gathered for the purpose of establishing rules of justice which are as fair as possible. The participants must be rational and self-interested. They must be able to calculate the consequences of their decisions, but they must not know how any of the proposed alternatives will affect their own particular interests. In this so-called "original position" no one is able to act on personal biases. For example, in making rules for just behavior in a medical emergency the rule makers would not know whether in fact they might be patients or physicians. With this perspective in mind Rawls offers the following principle:

> Paternalistic decisions are to be guided by the individual's own settled preferences and interests insofar as they are not irrational. . . . As we know less and less about a person, we act for him as we would act for ourselves from the standpoint of the original position. We try to get for him the things he presumably wants whatever else he wants. We must be able to argue that with the development or the recovery of his rational powers the individual in question will accept our decision on his behalf and agree that we did the best thing for him.[19]

In acting for someone as "we would act for ourselves from the standpoint of the original position," an attempt would be made to make choices with which a rational and prudent person would likely agree. The central concern is *not* the probability that the *actual* person in question will retrospectively agree with the decisions. The crucial point is that the decisions must be justifiable to a theoretical third party—a *reasonable person* in the patient's position.

This ethical principle provides no specific content for decisions, but it does give a basis on which emergency medical decisions can be made. It protects physicians from a patient who, on the basis of idiosyncratic preferences, disagrees with the decisions which have been made. It also pro-

tects a patient from a physician who adheres to norms differing from those expected of a representative reasonable person.

Is the established emergency procedure of preserving life whenever possible in harmony with the above principle? In order to assert that it is, we must assume that most reasonable people wish to go on living. Whatever values are maintained, the one "good" which is essential to the realization of nearly all others is life itself. This does not mean that life is the highest good or an absolute good in the "vitalistic" sense. Rather, life is seen as a relative good which is, nevertheless, basic and precious—a value that ought to be preserved as requisite for other values.

Even if the decision to commit suicide might be deemed rational in some situations, it seems virtually impossible in emergency medicine to take such a consideration into account. One might imagine a case in which a person who had apparently attempted suicide would be accompanied by a family member to the emergency room. The family member might produce a suicide note and show evidence of an overdose of a particular drug. Even if the legal restrictions prohibiting a physician's involvement as an accomplice in a suicide could be set aside, the physician would still find it necessary to decide in favor of the preservation of life. There would be no time to seek answers to absolutely essential questions. The physician could not determine, for example, whether the patient might not actually be the victim of an attempted homicide. Acting on a bias in favor of life would seem to be the most reasonable course under the circumstances.

Summary

Practical obstacles to the use of informed consent in emergency medicine often necessitate the exclusion of a patient's participation in the decision-making process. A principle has been sought which will take into account both respect for the personal autonomy of a patient and the need to make paternalistic decisions. Decisions made from the standpoint of the "original position" appear to satisfy these requirements by resorting to the theoretical standards of unbiased *reasonable persons*. In practice, decisions made in favor of preserving life, irrespective of the patient's expressed consent, are justifiable on this basis. The rapid pace of emergency care cannot take into account the idiosyncratic wishes of desperately ill persons when many factors which in all likelihood have interfered with rational thinking are present. Emergency life-preserving measures taken by the physician seek ultimately to restore patients' autonomy. Under more stable circumstances a better evaluation of patients' capacity for decision-making can be achieved. No longer under the influence of immediate physical and emotional trauma, patients should then be able to make choices that better reflect their concerns and goals.

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Refer to: Wagner MS: A summer preceptorship experience (From a Medical Student). West J Med 126:160-163, Feb 1977

A Summer Preceptorship Experience

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*Editor's Note: The CMERF-SCOPE (California Medical Education and Research Foundation-Student Community Orientation Preceptorship Education) program is now in its fourth year of operation as a private, nonuniversity-affiliated, summer experience in primary care for first-year and second-year medical students. Established to provide preclinical students with direct exposure to day-to-day medical practice in California communities, 127 students, 81 physicians and 65 hospitals have participated during the first three years. Evaluation by both physicians (preceptors) and students (preceptees) offers striking evidence that SCOPE has provided valuable insights into the world of medicine outside academia, including the organization and delivery of health care in communities. The program has also exposed medical students to realistic situations that can help them make sound career decisions.**

MANY MEDICAL SCHOOLS provide a summer break between the first and second years. Often, first year medical students look to the summer as a period of recuperation or even a well-deserved reprieve. Having completed my first year of medical school last spring, I recall having precisely these feelings. However, at the same time I had to be realistic; I wanted to schedule something that would keep me active as well as meet my financial needs. This meant getting out and hustling for summer employment, if at all possible in the health field.

It was in February that I heard of a program established two years earlier under the auspices of the California Medical Association, and sponsored by the California Medical Education and Research Foundation (CMERF). The SCOPE—Student Community Orientation Preceptorship Education—program was established as an innovative summer preceptorship program offering pre-clinical medical students realistic insight into the world of medicine outside academia.

The selection process for this program is by lottery, with some 200 medical students applying for about 40 positions. During the spring break in March, I learned that fortune had provided me a summer preceptorship position at the Antelope Valley Hospital Medical Center (AVHMC) in Lancaster, California. I was doubly pleased, since my employment efforts had to that time been unsuccessful. I accepted immediately, but I had some apprehension because it appeared that the stipend I would be offered ($800 for the months of July and August) would cover my summer living expenses but would leave me little to credit toward my next year's school expenses. But I soon learned that one of the physicians in Lancaster was gracious enough to allow another student and me to stay in his home during our two-month preceptorship in Lancaster. It is my sincere hope that those who read this will be inspired to institute a SCOPE preceptorship in their own community, and make it possible for more medical

*A complete report of the program as a whole, The CMERF-SCOPE Program: A Medical Student Preceptorship in Primary Care, Socioeconomic Report Vol. XVI, No. 4, June 1976, is available from the Bureau of Research and Planning, Division of Research and Socioeconomics, California Medical Association, 731 Market Street, San Francisco, CA 94103.

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ABBREVIATIONS USED IN TEXT

AVHMC = Antelope Valley Hospital Medical Center
CMERF = California Medical Education and Research Foundation
SCOPE = Student Community Orientation Preceptorship Education

students to benefit from this unique experience.

The design of the preceptorship at AVHMC provided a basic orientation to several facets of private medical practice as well as a number of allied health fields. The original schedule as presented to me was:

July 1-2—Department orientation at AVHMC: General tour of facility followed by orientation to administration, dietary, engineering, business office, volunteer program, medical records, inhalation therapy, occupational therapy, pharmacy, social services.

July 5-9—Mental Health.

July 12-26—General surgery: Mornings—operating room; Afternoons—orientation to private office practices in orthopedics; ear, nose and throat; urology; neurosurgery.

July 17—Orientation to chaplaincy service at AVHMC.

July 19-25—Family practice.

July 26-30—Obstetrics and gynecology.

August 2-8—Emergency room.

August 6—Los Angeles County paramedics.

August 9-13—Pediatrics.

August 16-20—Elective: neurosurgery.

August 23-27—Internal medicine.

August 25—Alcoholic Rehabilitation Center.

August 30—Los Angeles County Health Department Venereal Disease Clinic and family planning.

August 31—Renal Dialysis at the University of California, Los Angeles-AVHMC Family Practice Center, Los Angeles County Well-Baby Clinic.

Happily, such a schedule offered an opportunity to experience a wide variety of new things. My physician program director at AVHMC wished to provide a basic orientation to the administrative aspects of operating a hospital, as well as to basic medical discipline, and to a variety of subspecialties, at both the clinical and private practice levels.

Many readers will undoubtedly wonder just what the role of an extern really is. I will relate the role I assumed, but nevertheless would point out that it varies tremendously from student to student, depending on both the responsibilities the student wishes to accept and those that the preceptor makes available. Basic, however, to all students in the program is a short affidavit entitled "Legal Aspects of Student Performance of Medical Procedures under the CMERF-SCOPE Program in California." The document merely issues some important legal guidelines; otherwise the student and the preceptor are on their own to develop a mutually satisfying program. In any case, the best way to answer questions about the extern's role is to give some specific experiences from my externship at AVHMC.

The first two days of the program involved a general orientation to the various hospital departments. I became acquainted with administrative personnel and departmental directors whom I would repeatedly see throughout the summer and was introduced to the departmental responsibilities within the overall operation of a hospital. It was fascinating to observe the variety of skilled personnel required to run a hospital safely and efficiently.

During these two days a short tour was made of Lancaster Convalescent Hospital, adjacent to AVHMC. It was interesting to compare how the two facilities are operated. Of course, only a superficial awareness could be obtained in such a short time available. Nevertheless, it established a framework to view similar administrative roles and responsibilities in the future.

My clinical experience this summer ranged from helping apply bandages in the emergency room to scrubbing for surgery and assisting in any manner the surgeon thought appropriate, which usually involved holding retractors or cutting stutures. Generally, I can best describe my clinical role as that of an observer. I was present to assist in any way I could, but for the most part I approached the experience as a student curious about each case presented and naive about how to deliver treatment. The experience was a firsthand exposure to the art of correlating basic science and clinical skills.

At no time did I chart my observations or findings, though I always seized the opportunity to discuss them with the physician. Likewise, I never wrote orders or prescribed medications, but would inquire why a particular drug or therapy was ordered. Surprisingly enough, most physicians freely offered explanations at a level of understanding coincident with my training. I was

pleased to find so many private physicians so willing to give of their time to answer questions. The physicians were happy to have the opportunity to impart some of their experience to someone just beginning medical training.

As a clinical example of my externship, I will tell about my experience in the Mental Health Ward and Psychiatric Service. I began the week assisting an accredited psychiatric technician prepare initial evaluations to the staff psychiatrist and then would meet with the patient in consultation with the psychiatrist. Finally, we would discuss the case. This permitted me to acquire insight that I would not normally have received devoting all my time to interacting with the patients in a purely nonclinical fashion. I also observed the roles of occupational therapist, nursing technician and other staff personnel, and their attention to the particular needs of each mental health patient from a different perspective.

With the patients' permission, I also had the opportunity to sit in on several private office cases, and discovered the real manner in which a psychiatrist conducts a private practice. On one occasion I was requested to do the initial workup of a patient and present my findings to the psychiatrist before his evaluation. I found that I had acquired some useful interview techniques earlier in the week which allowed me to suspect a diagnosis that the psychiatrist later confirmed.

My surgical rotation was one of the most rewarding weeks all summer. Mornings I was free to follow the surgery schedule and scrub for any case approved by the surgeon. I was fortunate that there was no case I was not permitted to observe. I was often requested by the surgeon to assist in irrigation, aspiration, traction, cauterization or cutting sutures. Primarily, my role was that of a curious student having just finished gross anatomy but having had no exposure to human surgical anatomy. I was quizzed about my understanding of anatomy, and when my memory failed surgeons quickly refreshed it. They, as well as I, were aware that what was now refreshed would not be soon forgotten. Throughout the week I observed some 20 procedures ranging from an appendectomy to a craniotomy. As far as more practical experience is concerned, I learned basic sterile techniques, scrub techniques and so forth. Surely, this is also learned in medical school, but learning it first hand in a preceptorship gives it a special significance.

Another particularly rewarding week for me was spent in the emergency room. It was here that I became aware of the vast variety of cases for which people seek care or hesitate to seek care. Here again my role was primarily that of an observer. When things were busy, there was no time to inquire why a particular treatment was being given. Instead, I put myself to work doing tasks that I had seen done earlier in the week and felt confident to carry out—for example, assisting in skin grafting. I also found myself answering many questions the patients had that I knew I could answer. I established a criterion for myself that would not jeopardize the patient or the hospital, and always made certain I had the emergency physician's authorization. It was in this way that I acquired a new sense of responsibility about what I could confidently do and what I could not do at my particular level of training.

My week externships in family practice, obstetrics and gynecology, pediatrics and internal medicine were as fulfilling as those in surgery, emergency medicine and psychiatry. In fact, each rotation provided a unique opportunity to gain both clinical and practical information in each specialty.

Besides the clinical experience at AVHMC during my various rotations, I also had opportunities to visit other hospitals and clinics in the Antelope Valley area, such as Lancaster Community Hospital, Palmdale General Hospital, Edwards Airforce Base Hospital, Ridgecrest Community Hospital and Ridgecrest Medical Clinic. Additionally, the externship at AVHMC included attending service and review committees, staff meetings and continuing education conferences. It was through attending these committee meetings and conferences that I learned about peer review, policy making and continuing education, and realized that they too are integral parts of a private physician's responsibilities to both his hospital staff and the community he serves.

Exposure to various allied health professions was also worthwhile and rewarding, since it expanded my awareness of the need for medical personnel outside the realm of both academia and private practice. An opportunity to investigate such areas would seldom present itself in medical school unless a student were particularly interested in the field of public health.

Perhaps the best way to illustrate the enthusiasm shown by the community of Lancaster for the preceptorship program is to give some comments made by several physicians when they

were asked what they thought about the program and its goals.

"I thought it was very worthwhile. Looking back on my own medical experience, the first time I found out what a fellow did in private practice was when I was in private practice . . . I think it's good to have a fellow spend a considerable amount of his time being rotated through various private doctor's offices, to give him a feel of what medicine is. It's really not what you find in medical school."

"I was very happy to have you. I recall finishing my own training and realizing I had been trained to be an ivory tower diagnostician working in a university hospital. That's what I knew about the practice of medicine, and I wasn't satisfied with that. I found this summer a fine opportunity to try to show you an entirely different area of practice and get you exposed to that idea. Because I didn't know anything about the private practice of medicine outside the ivory tower until I was discharged . . . I would have given anything to have had the opportunty to run around and get into a G.P.'s office and see what was going on, to get out and see what a surgeon really did, and to see what a private physician really did with his time. . . . "

"When I came to Lancaster I was somewhat like you are as a preceptee, because I had never practiced anywhere other than in my present specialty. So what the quality of medicine was away from the city and away from the university training center was a real curiosity to me, particularly in terms of how comfortable I would feel there. And I think overall I found that the caliber of medicine practiced in a place like this was as good as anywhere I had been otherwise, partly because of the burden to be versatile on the part of the people who are here and the burden to be responsible in different areas of medicine."

"Some of the best questions I ever get asked are not from doctors, not from my fellow associates, but from students who come and ask these tough embarrassing questions . . . and I have to justify what I've done. I have to do it for myself too, of course, but it gets even more pointed when these youngsters who still remember some of their basic science start asking some questions—some intelligent ones."

"And there is another feature to this issue. As you go along through the years you develop effective practical ways of doing things but you never have the chance to tell anybody why they are so much better than the original way you were taught to do them—by the book or whatever. A preceptor comes along and when you do something which you feel you've learned and reflects your experience he asks, 'Why did you do it that way?'. And you can give it to him. You'll never write a paper about it, you'll never teach it in medical school; but you really think it's valuable, so you pass it on to a fresh person. There's something about that that makes you feel good."

One physician summed up my exact sentiments when he said: "I think such a program is a real benefit for a beginning medical student. Medical school training is usually so idealistic in nature, and the clinical cases presented are so selective. However, you've undoubtedly been exposed this summer to what the real outside world of practicing medicine is all about, not so much from a clinical standpoint, but from a general overall perspective. Such an experience seems as though it would be a real benefit when you start considering what particular field of medicine you ultimately wish to pursue."

And finally, my physician program director had this to add: "Your experience this summer should have given you the opportunity to increase your confidence and rapport when seeing patients and working with physicians and other allied health personnel. And it has, I hope, helped you gain an admiration and respect for the nonmedical employees as well. It's given you an introduction to rural medicine which is not crude and backwoodsy as most people would have you think. I honestly believe the program is best suited to students after their first year, for it is then that they are most eager since every experience will be new and fresh and exciting."

I hope that by presenting these various comments of the physicians and by relating some of my own experiences this summer, more communities will be inspired to establish a SCOPE preceptorship in the future. Every medical student could benefit from being involved in such a program, and certainly physicians and the communities they serve would benefit too by sharing something that no one else has to share.

Special Article

Refer to: Oglesby AC, Goldstein H, Hexter AC, et al: Health insurance coverage of mothers and children (1974). West J Med 126:164-170, Feb 1977

Health Insurance Coverage of Mothers and Children (1974)

ALLAN C. OGLESBY, MD, MPH; HYMAN GOLDSTEIN, PhD; ALFRED C. HEXTER, MA, *and* HELEN M. WALLACE, MD, MPH, *Berkeley*

RAPID CHANGES have occurred in recent years that are having profound effects on the delivery of health care in the United States. Rapidly increasing cost of medical and hospital care has caused increased emphasis on ambulatory and preventive health services. Changing social values, such as attitudes toward family planning, abortion and sterilization, including vasectomy, have caused the development and acceptance of these as necessary health services. The increased value of health insurance as a bargaining issue for labor, the broader health coverage available in group plans, and expanding health coverage have increased the significant role played by health insurance in the United States.

The Health Insurance Institute statistics show[1] that private health insurance companies insure nearly nine of every ten Americans. In 1972 about 182 million Americans were covered by one or more forms of private health insurance. These statistics show that 143 million persons were covered against "regular" medical expenses at the end of 1972. More than 78 million were covered by private insurance companies, and 67 million were covered by Blue Cross/Blue Shield and other medical society-approved plans. Other health insurance plans covered 10 million persons.[1]

Hospital expense insurance provided coverage for 182 million persons at the end of 1972. Insurance companies covered 115 million persons (63 percent); Blue Cross/Blue Shield and other medical society-approved plans covered nearly 80 million persons (44 percent) and other plans covered some 9 million persons (5 percent).[1]

Of the 182 million covered by hospital insurance 105 million were dependents, usually the insured person's spouse and unmarried children.[1]

In 1972 a total of $21 billion in health insurance benefits was paid by private insurance organizations in the United States. More than $12 billion of the total (58 percent) was paid for hospital expenses. Blue Cross/Blue Shield and other hospital-medical plans paid almost $10 billion in health care benefits.[1]

The United States Department of Commerce reported that in 1972[2] personal consumption expenditures for health care, including all expenses for health insurance, totaled almost $75 billion. In all, national spending for health care amounted to $86.4 billion in fiscal year 1972. This is a per capita expenditure of $396 for personal health care.

From the Maternal and Child Health Program and Family Health Program, University of California School of Public Health, Berkeley.

Presented at the MCH Section of the Annual Meeting of the American Public Health Association, Chicago, Illinois, November 1975

This study was supported by Grant No. MC-R-060208-03-0 from the Maternal and Child Health Service, Office of Clinical Services, U.S. Department of Health, Education, and Welfare, Rockville, Maryland.

Reprint requests to: Helen M. Wallace, MD, Chairman, Maternal and Child Health Program and Family Health Program, University of California School of Public Health, Earl Warren Hall, Berkeley, CA 94720.

Because of the large role in health care played by health insurance, a study was undertaken to examine special health services for mothers and children covered by private health insurance and the Blue Cross/Blue Shield plans.

Methods

A questionnaire was prepared and pretested. This study form was mailed to all insurance companies in the United States that sell health insurance as listed in *The Insurance Almanac, 1973 (61st Annual Edition)*[3] and to all Blue Cross and Blue Shield Plans listed in the *1973 Argus Chart of Health Insurance—75th Annual Edition,* a National Underwriter publication.[4] Follow-up of nonrespondents was by subsequent mailings.

Results

Response

A total of 734 company names was included in the original mailing. Of these, 13 Blue Cross/Blue Shield and 139 others turned out to be duplicates (the same company doing business under more than one name), out-of-business or not at present selling health insurance, leaving a total of 582 companies in the sample—116 Blue Cross/Blue Shield and 466 others. The first mailing was in May, 1974, with four follow-up mailings. Questionnaires with information were received from 231 companies (39.7 percent). One hundred and seventy-seven responses were from private companies (38.0 percent) and 54 (46.6 percent) were from Blue Cross/Blue Shield companies. Of the companies 32 (5.5 percent) refused to fill out the study form, and 15 (2.6 percent) replied by letter rather than giving information on the questionnaire; the remainder did not reply (Table 1).

Maternity Care

Maternity care was provided by 53 (98.1 percent) of the reporting Blue Cross/Blue Shield companies and by 160 (91.4 percent) of the other respondent companies (Table 2). In order to examine maternity care coverage more thoroughly, this classification was divided into prenatal care, labor and delivery, and postpartum care.

TABLE 1.—*Type of Return by Type of Company*

Type of Return	Number of Companies: Total	Number of Companies: Blue Cross/Blue Shield	Number of Companies: Other	Percent: Total	Percent: Blue Cross/Blue Shield	Percent: Other
Total respondent companies	582	116	466	100.0	100.0	100.0
Questionnaire returned with information	231	54	177	39.7	46.6	38.0
Reply by letter	15	4	11	2.6	3.4	2.4
Refusal	32	4	28	5.5	3.4	6.0
No response	304	54	250	52.2	46.6	53.6

TABLE 2.—*Provision of Coverage by Type of Coverage and Type of Company*

Type of Coverage	Blue Cross/Blue Shield Companies: Respondent Companies	Blue Cross/Blue Shield Companies: Number Providing Coverage	Blue Cross/Blue Shield Companies: Percent Providing Coverage	Other Companies: Respondent Companies	Other Companies: Number Providing Coverage	Other Companies: Percent Providing Coverage
Catastrophic illness	54	52	96.3	174	142	81.6
Maternity care	54	53	98.1	175	160	91.4
Prenatal care	51	44	86.3	165	79	47.9
Labor and delivery	53	53	100.0	170	153	90.0
Postpartum care	51	47	92.2	167	90	53.9
Family planning	54	4	7.4	168	9	5.4
Abortion	53	49	92.5	175	123	70.3
Sterilization	54	49	90.7	167	106	63.5
Male	54	49	90.7	164	115	70.1
Female	54	49	90.7	165	114	69.1
Hospital newborn care	54	50	92.6	174	106	60.9
Health care of well children	54	23	42.6	168	38	22.6
Health care of sick children	54	53	98.1	175	157	89.7
Health care of children with chronic or handicapping conditions	54	51	94.4	173	142	82.1
Psychiatric care	54	53	98.1	174	131	75.3
Accidents	54	54	100.0	176	176	100.0
Other	34	27	79.4	113	73	64.6

Prenatal Care

Prenatal care was provided by 44 (86.3 percent) of the respondent Blue Cross/Blue Shield companies, but by only 79 (47.9 percent) of other respondent companies (Table 2).

Only one (1.9 percent) of the Blue Cross/Blue Shield respondents reported that there is no time time period after enrollment before maternity care is covered; 53 (98.1 percent) limit maternity care coverage to conception that occurs after the policy becomes effective. The other companies responding indicated that 28 (17.1 percent) have no time period before coverage of maternity care begins, 117 (71.3 percent) limit maternity coverage to conception that occurs after the policy becomes effective, and 19 (11.6 percent) have other time limitations after enrollment before maternity care becomes effective.

During the prenatal period, 23 (44.2 percent) of the responding Blue Cross/Blue Shield companies have no exclusion of any indicated laboratory tests, and 96 (61.5 percent) of other responding companies have no such exclusions.

Coverage for hospital care during the prenatal period is provided by 44 (89.8 percent) of the respondent Blue Cross/Blue Shield respondents, and by only 112 (71.3 percent) of other respondent companies.

Labor and Delivery

All Blue Cross/Blue Shield respondents covered labor and delivery, but only 153 (90 percent) of the other responding companies did (Table 2).

Of the responding Blue Cross/Blue Shield companies providing labor and delivery coverage, 40 (76.9 percent) have a limit on the amount paid for delivery, and 138 (84.7 percent) of the other respondent companies have these limits. Of the Blue Cross/Blue Shield companies reporting, 45 (95.7 percent) provide coverage for medical complications of labor and delivery, but only 123 (79.9 percent) of other responding companies provide such coverage.

TABLE 3.—*Coverage for Abortion and Sterilization by Type of Company*

Type of Coverage	Blue Cross/Blue Shield Companies			Other Companies		
	Respondent Companies	Number Providing Coverage	Percent Providing Coverage	Respondent Companies	Number Providing Coverage	Percent Providing Coverage
Therapeutic abortion	53	49	92.5	169	125	74.0
Abortion on request	50	43	86.0	171	95	55.6
Sterilization on request	50	44	88.0	171	94	55.0
For both men and women	..	42	84.0	..	89	52.0
For men only	..	0	0.0	..	3	1.8
For women only	..	2	4.0	..	2	1.2

TABLE 4.—*Hospital Coverage of Newborn Infants by Type of Company*

Type of Coverage	Blue Cross/Blue Shield Companies			Other Companies		
	Respondent Companies	Number Providing Coverage	Percent Providing Coverage	Respondent Companies	Number Providing Coverage	Percent Providing Coverage
Newborn usually covered from time of birth	54	53	98.2	175	98	56.0
Unqualified	..	50	92.6	..	82	46.9
Qualified	..	3	5.6	..	16	9.1
Well newborn						
Nursery care	54	48	88.9	142	72	50.7
Rooming-in	53	22	41.5	141	40	28.4
Sick newborn						
Observation nursery care for congenital malformations	54	52	96.3	143	132	92.3
ICU for congenital malformations	54	52	96.3	143	135	94.4
Observation nursery care for low birthweight infants	54	50	92.6	143	114	79.7
ICU for low birthweight infants	54	49	90.7	143	117	81.8
Observation nursery care for other sick infants	54	51	94.4	143	132	92.3
Isolation nursery for other sick infants	54	51	94.4	143	133	93.0
ICU for other sick infants	54	51	94.4	143	130	90.7

ICU = intensive care unit.

Postpartum Care

Postpartum care was covered by 47 (92.2 percent) of the responding Blue Cross/Blue Shield companies, but by only 90 (53.9 percent) of the other companies responding (Table 2).

The responding Blue Cross/Blue Shield companies reported that 30 (57.7 percent) have a limit on the number of hospital days covered for postpartum care, while only 56 (36.1 percent) of the others responding have such time limits.

Consultant services are included as part of postpartum coverage by 37 (75.5 percent) of Blue Cross/Blue Shield respondents and by 100 (64.1 percent) of other respondents. Care of complications in the postpartum period is covered by most responding Blue Cross/Blue Shield companies, 50 (96.2 percent), and by 130 (81.3 percent) of other responding companies.

Family Planning—Abortion—Sterilization

The service provided by the smallest number of respondents was family planning with only 4 (7.4 percent) of the reporting Blue Cross/Blue Shield companies and 9 (5.4 percent) of the other responding companies providing coverage for these services (Table 2).

However, 49 (92.5 percent) of the responding Blue Cross/Blue Shield companies provided for abortion, 49 (92.5 percent) provided for therapeutic abortion and 43 (86 percent) provided for abortion upon request. Of the other companies reporting, 123 (70.3 percent) had coverage for abortion, 125 (74 percent) provided for therapeutic abortion and only 95 (55.6 percent) had coverage for abortion upon request (Tables 2 and 3).

Coverage for sterilization was included by 49 (90.7 percent) of the responding Blue Cross/Blue Shield companies, and by 106 (63.5 percent) of other respondent companies. There was no significant difference between coverage for sterilization of men and women (Table 2). Sterilization upon request was covered by fewer companies in both categories: by 42 (84 percent) of Blue Cross/Blue Shield companies and by 89 (52 percent) of other companies (Table 3).

Newborn Services

Of the companies reporting, 132 (57.6 percent) provided unqualified coverage of newborns from the time of birth. There were 50 (92.6 percent) of the responding Blue Cross/Blue Shield companies who provided unqualified newborn coverage and only 82 (46.9 percent) of the other companies. Nursery care for well newborns was covered by 48 (88.9 percent) of the responding Blue Cross/Blue Shield companies and 72 (50.7 percent) of the other responding companies. It is interesting to note that only 22 (41.5 percent) of the responding Blue Cross/Blue Shield companies and 40 (28.4 percent) of other responding companies covered rooming-in for newborn infants (Table 4).

Coverage for sick infants was generally better by all reporting companies. Observation and newborn intensive care for congenital malformations was covered by almost all (96.3 percent) responding Blue Cross/Blue Shield companies. Other responding companies reported that 132 (92.3 percent) included coverage of observation nursery care and 135 (94.4 percent) included newborn intensive care unit services for congenital malformations (Table 4).

Coverage for low birth weight infants in an observation nursery was included by 50 (92.6 percent) of responding Blue Cross/Blue Shield companies and 114 (79.7 percent) of other companies responding. However, newborn intensive care unit coverage for low birth weight infants was covered by 49 (90.7 percent) of responding Blue Cross/Blue Shield companies and only 117 (81.8 percent) of the others responding.

Most of the reporting companies provided coverage for observation nursery care of other sick infants (92.9 percent), isolation nursery care of sick infants (93.4 percent) and newborn intensive care unit services for sick infants (91.9 percent) (Table 4).

Children

Although there is increasing acceptance of well child care as essential for adequate health maintenance, only 23 (42.6 percent) of the responding Blue Cross/Blue Shield plans and 38 (22.6 percent) of other respondents provided such coverage (Table 2).

Of the 23 responding Blue Cross/Blue Shield companies providing well child care, less than half provided coverage for hearing screening (40 percent), developmental screening (37.5 percent) or multiphasic screening (42.9 percent); slightly more than half covered vision screening (52.9 percent). Dental prophylaxis and fluoride application are covered by ten companies reporting (62.5 percent), while orthodontia is provided for only seven (46.7 percent). Immunizations are

included by ten (62.5 percent), tuberculin testing by nine (60 percent) and only four (25 percent) will cover intelligence testing (Table 5).

Of the 38 other insurance companies responding that provide well child services, only six (35.3 percent) cover hearing screening, three (17.6 percent) provide for developmental screening, five (29.4 percent) cover multiphasic screening and eight (47.1 percent) provide coverage for vision screening. Dental prophylaxis is included by ten (58.8 percent), fluoride application by nine (52.9 percent) and orthodontia by only five (29.4 percent) of those responding. Immunizations are covered by only nine (56.3 percent), tuberculin testing by ten (58.8 percent) and intelligence testing by only three (17.6 percent) (Table 5).

Of the total respondents who provide coverage for well child care, 10 (66.7 percent) of Blue Cross/Blue Shield plans and 14 (46.7 percent) of other companies limit the number of visits for such care (Table 6).

Coverage for sick child care is provided by all except one of the respondent Blue Cross/Blue Shield companies (98.1 percent); only 51 (94.4 percent) offer coverage of health care for children with chronic or handicapping conditions. Of the other respondent companies, 157 (89.7 percent) offer health care for sick children, and 142 (82.1 percent) provide coverage for health care of children with chronic or handicapping conditions (Table 2).

The number of ambulatory visits to a physician is limited by 47 (24.7 percent) of all companies reporting. Thirteen (30.2 percent) of the Blue Cross/Blue Shield companies and 34 (23.1 percent) of other companies limit the number of visits to physicians.

A total of 169 companies reported on coverage for outpatient psychiatric care and 187 for inpatient psychiatric care. Visits for outpatient psychiatric care were limited by 35 (79.5 percent) of Blue Cross/Blue Shield plans and by 95 (76 percent) of the other companies. Inpatient visits were limited by 37 (72.5 percent) of the Blue Cross/Blue Shield companies and by 62 (45.6 percent) of the other companies (Table 6).

TABLE 5.—*Coverage for Well Child Care by Type of Coverage and Type of Company*

	Blue Cross/Blue Shield Companies			*Other Companies*		
Type of Coverage	*Respondent Companies*	*Number Providing Coverage*	*Percent Providing Coverage*	*Respondent Companies*	*Number Providing Coverage*	*Percent Providing Coverage*
Coverage for well infants, children or adolescents	54	16	29.6	173	18	10.4
Visits to physician	16	14	87.5	17	10	58.8
Dental prophylaxis	16	10	62.5	17	10	58.8
Dental fluoride application	16	10	62.5	17	9	52.9
Orthodontia	15	7	46.7	17	5	29.4
Vision screening	17	9	52.9	17	8	47.1
Hearing screening	15	6	40.0	17	6	35.3
Developmental screening	16	6	37.5	17	3	17.6
Multiphasic screening	14	6	42.9	17	5	29.4
Intelligence test	16	4	25.0	17	3	17.6
Tuberculin test	15	9	60.0	17	10	58.8
Pregnancy test	15	5	33.3	17	5	29.4
Immunizations	16	10	62.5	16	9	56.3
X-ray studies	17	15	88.2	18	13	72.2
Laboratory services	17	15	88.2	17	13	76.5

TABLE 6.—*Limitations on Number of Visits for Well Child Care, Outpatient Visits by Sick Children to Physicians, and Inpatient and Outpatient Visits by Sick Children for Psychiatric Care, by Type of Company*

	Blue Cross/Blue Shield Companies			*Other Companies*		
Type of Coverage	*Respondent Companies*	*Number of Visits Limited*	*Percent of Visits Limited*	*Respondent Companies*	*Number of Visits Limited*	*Percent of Visits Limited*
Visits for well child care	15	10	66.7	30	14	46.7
Outpatient visits of sick children to physicians	43	13	30.2	147	34	23.1
Outpatient visits of sick children for psychiatric care	44	35	79.5	125	95	76.0
Inpatient visits of sick children for psychiatric care	51	37	72.5	136	62	45.6

Cancellation of Policies and Basis for Payment

Of the 210 respondents to the question regarding cancellation of policies, 71 (33.8 percent) reported that policies are not subject to cancellation by the insurer, 46 (21.9 percent) can be cancelled for nonpayment and 93 (44.3 percent) reported that policies can be cancelled for reasons other than nonpayment.

Of 197 respondents, 19 (38 percent) of Blue Cross/Blue Shield and 77 (52.4 percent) of other companies pay on an indemnity basis. There were 38 (80.9 percent) of Blue Cross/Blue Shield and 121 (79.1 percent) of other companies that usually pay on a "usual, customary and reasonable" basis.

Peer Review

Of the Blue Cross/Blue Shield respondents, only 6 (12.8 percent) do not have medical advisors for peer review, 38 (79.2 percent) use local medical society peer review committees and 29 (63 percent) utilize the State Medical Association Peer Review Appeals Committee. The other companies responding reported that 79 (48.8 percent) do not have medical advisors for peer review, 73 (45.6 percent) utilize local medical society peer review committees and 67 (42.7 percent) use the State Medical Association Peer Review Appeals Committee.

Discussion

The type of company providing the policy influences the coverage that is provided. Throughout this study on almost every item the Blue Cross/Blue Shield companies provide coverage for more preventive services and comprehensive care for mothers and children. This type of company is nonprofit, which suggests that more of the premium paid can be returned in benefits.

Since the early 1960's there has been an increasing emphasis on the benefits of comprehensive health care services for mothers and children. The concept of health maintenance based on preventive care rather than episodic, crisis-oriented health care has been shown to be valid by many demonstrations.[5-8] Federally funded Maternal and Infant Care Projects (MIC), Children and Youth Projects (C and Y), Neighborhood Health Centers and privately financed plans such as the Kaiser Foundation Health Plan have proved on a limited population that comprehensive health care is feasible, even with high risk populations. The limitations today are mainly due to financing, manpower and accessibility to comprehensive health care.

It is clear that most individual persons and families in the United States need health insurance coverage for catastrophic illness and acute medical care. It is also true that the rising cost of care for adequate health insurance may mean fewer people will be covered under the present system. Until we can find a means of providing comprehensive preventive services,* especially to infants, children, adolescents and women of childbearing age, the need for crisis-oriented services will continue to exist and will not diminish.

Data in this study show that while maternity care was offered by more than 90 percent of all respondents, the degree of coverage and its limitations were revealed when maternity care was analyzed into some of its components. As shown in Table 2, less than half (47.9 percent) of respondent companies other than Blue Cross/Blue Shield cover prenatal care as part of the maternity benefits. This type of limited policy does little to encourage early detection of complications or high risk pregnancies. Of those companies covering prenatal care, about 10 percent of Blue Cross/Blue Shield and almost 30 percent of other respondent companies do not provide coverage for hospital care during the prenatal period.

While most companies provide coverage for labor and delivery, less than 5 percent of Blue Cross/Blue Shield and 20 percent of other respondent companies do not offer coverage for complications of labor and delivery. Since coverage of complications is widely found, it implies that this benefit is seen as one that most women of childbearing age need as a part of maternity care coverage. It is not known whether this means more concern for prevention, or that additional maternity benefits are offered because of lower utilization of this benefit.

Postpartum care is generally accepted by physicians as necessary preventive care in comprehensive maternity care. Such care is covered by 92.2 percent of the Blue Cross/Blue Shield plans but only by 53.9 percent of other companies.

Restrictions of benefits in maternity coverage may indicate that some companies hold the point of view that different phases of childhearing have varying degrees of importance to the health of

*This means continuous health supervision, which includes health appraisal (medical examinations and screening tests), immunizations, dental health, health education, and safety and accident prevention for women, children and youth.

the mother and her child. Certainly, such restrictions do not encourage comprehensive health care for mothers during childbearing. Complications of pregnancy can be catastrophic financially to the young family. There is an unmet need in our present health insurance system for coverage of all aspects of childbearing offered in such a way that it can be available to all women of childbearing age.

As social progress has brought about significant attitudinal and legal changes as well as availability of family planning, abortion and sterilization upon request, including vasectomy, it is interesting to see how these changes have been reflected in health insurance coverage. Few companies reported providing benefits that cover family planning services: only 7.4 percent of Blue Cross/Blue Shield companies and 5.4 percent of other compnies. While 86 percent of Blue Cross/Blue Shield companies cover abortion upon request, slightly more than half (55.6 percent) of other companies do so. There was no significant difference in coverage for male and female sterilization. There was a large difference in coverage for sterilization by Blue Cross/Blue Shield (84 percent) and other companies (52 percent).

The coverage of such innovative services as individual and family health education as part of ambulatory health care is not included in most health care insurance. Such service would be invaluable for many, such as women during pregnancy, a family with a developmentally disabled child or teenagers with serious health problems such as diabetes.

Throughout the health delivery system in the United States, there has been increasing concern regarding quality of services provided and appropriate utilization of health care services. Peer review is becoming more accepted by physicians as a useful and reasonable way to accomplish some periodic surveillance of both utilization and quality of services. While this approach is relatively recent, it appears that less than half of those insurance companies not associated with medical societies have used this method of review.

This paper provides data on the extent of coverage for health services for mothers and children, reported by health insurance companies. The study does not include data on outcome of such coverage, utilizing such indices as mortality and morbidity, comparing patients covered by such health insurance policies with patients without such policy coverage.

Summary and Conclusions

This study shows that there is a significant difference in health coverage provided by the different types of companies that responded. The Blue Cross/Blue Shield plans almost always provided broader coverage of health care for mothers and children. Since greater than 60 percent of the population covered by health insurance is covered by companies other than Blue Cross/Blue Shield, it is evident that a large number of mothers and children have limited health coverage.

The uneven type of health care coverage reported by the respondents for maternity care and for infants, children and youths does not promote comprehensive health care. Preventive approaches to health services have limited coverage by health insurance generally.

Even though health insurance has increased in importance as a bargaining tool for labor and even though group plans have allowed for greatly expanded coverage, health care coverage in the United States still does not provide for total comprehensive health maintenance for many mothers and children. As we move toward a national health insurance plan, it will be a challenge to the health insurance industry to offer alternatives that will provide for comprehensive preventive and health care services for the mothers and children.

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ARTICLES TO READ IN OTHER JOURNALS

EDITOR'S NOTE: *From time to time members of the Editorial Board call attention to articles in other journals which they consider to be particularly significant. The editors believe these titles together with a brief assessment of the articles are worth publishing for the information of our readers.*

Microinvasive Carcinoma of the Uterine Cervix: A Long-term Follow-up of Eighty Cases

Christopherson WM, Gray LA, Parker JE

Cancer
38:629-632, Aug 1976

DISCIPLINES: Pathology, Obstetrics and Gynecology, General Medicine

READABILITY: Very good

A carefully done study of microinvasive carcinoma of the cervix which shows that simple hysterectomy would seem to be the treatment of choice. Although there is controversy as to the depth of invasion acceptable as microinvasion, these authors included cases with up to 5 mm of stromal invasion.

—RICHARD L. KEMPSON, MD
Stanford, CA

The VA Cooperative Randomized Study of Surgery for Coronary Arterial Occlusive Disease—II. Subgroup with Significant Main Lesions

Takaro T, Hultgren HN, Lipton MJ, et al

Circulation
54(Supplement III):107-117, Dec 1976

DISCIPLINES: Internal Medicine, Cardiology, Cardiovascular Surgery

READABILITY: Good

These results are from a randomized prospective study of coronary bypass surgical procedures. A substantial improvement in prognosis was shown in patients with symptomatic main left coronary disease with surgical treatment. This is an important paper, with careful analysis of data.

—J. DAVID BRISTOW, MD
Seattle

Risk for Breast Cancer Development Determined by Mammographic Parenchymal Pattern

Wolfe JN

Cancer
37:2486-2492, May 1976

DISCIPLINES: General Medicine, Surgery, Gynecology, Radiology

READABILITY: Good

Mammographic parenchymal pattern of the breast is placed in four categories that permit prediction of risk of carcinoma. The highest risk category shows 22 times greater incidence of carcinoma. Seventy-six percent of breast cancer would be found by screening 27 percent of the population.

—ROBERT B. ENGLE, MD
Laguna Beach, CA

Mortality in Depressed Patients Treated with Electroconvulsive Therapy and Antidepressants

Avery D, Winokur G

Archives of General Psychiatry
33:1029-1037, Sep 1976

DISCIPLINE: Psychiatry

READABILITY: Very good

Presents results of three-year follow-up study of 519 patients (plus summarizing literature and results in 4,333 other patients, or a total of 4,852 patients). Generally electroshock therapy is found best—that is, associated with least mortality from all causes.

J. M. STUBBLEBINE, MD
Greenbrae, CA

X-ray Pelvimetry of the Pregnant Adolescent

Aiman J

Obstetrics and Gynecology
48:281, Sep 1976

DISCIPLINES: Obstetrics and Gynecology, Family Practice

READABILITY: Good

An excellent evaluation of the bony pelvis that points out the hazards and pitfalls of pregnancy in adolescents.

—RALPH W. HALE, MD
Honolulu

Tumor Immunology

Pattello R

Obstetrics and Gynecology
48:374, Sep 1976

DISCIPLINE: Obstetrics and Gynecology

READABILITY: Good

A concise summary of the newer concepts of immunology as they relate to tumor biology and immunotherapy.

—RALPH W. HALE, MD
Honolulu

New Nomenclature for Vulvar Disease

International Society for the Study of Vulvar Disease

Obstetrics and Gynecology
47:122-124, Jan 1976

DISCIPLINES: Obstetrics and Gynecology, Dermatology, Pathology

READABILITY: Good

Presentation of a sensible and easily understood terminology for vulvar diseases. It is to be hoped that this terminology will be used by all concerned physicians.

—RICHARD L. KEMPSON, MD
Stanford, CA

in memoriam

Barr, Arthur L., San Diego. Died December 10, 1976 in San Diego, aged 84. Graduate of the Creighton University School of Medicine, Omaha, 1915. Licensed in California in 1926. Dr. Barr was a retired member of the San Diego County Medical Society.

Burnett, William Clemons, Berkeley. Died December 31, 1976 of heart disease, aged 70. Graduate of Meharry Medical College, Nashville, 1933. Licensed in California in 1947. Dr. Burnett was a member of the Alameda-Contra Costa Medical Association.

Dennis, Howard O., Palm Springs. Died May 18, 1976 of carcinoma of the stomach, aged 79. Graduate of the University of Illinois College of Medicine, Chicago, 1922. Licensed in California in 1922. Dr. Dennis was a retired member of the Riverside County Medical Association.

Duemling, Werner W., San Diego. Died December 30, 1976 in San Diego, aged 78. Graduate of the University of Michigan Medical School, Ann Arbor, 1924. Licensed in California in 1946. Dr. Duemling was a retired member of the San Diego County Medical Society.

Fricke, John William, San Francisco. Died December 24, 1976 in San Francisco, aged 71. Graduate of the University of Illinois College of Medicine, Chicago, 1935. Licensed in California in 1938. Dr. Fricke was a retired member of the San Francisco Medical Society.

Fuglie, Carl Stewart, Arcadia. Died November 22, 1976, aged 37. Graduate of the University of California at Los Angeles, School of Medicine, 1966. Licensed in California in 1967. Dr. Fuglie was a member of the Los Angeles County Medical Association.

Giovanazzi, Joseph E., San Diego. Died April 30, 1976 of heart disease, aged 63. Graduate of the University of Southern California School of Medicine, Los Angeles, 1938. Licensed in California in 1939. Dr. Giovanazzi was a member of the San Diego County Medical Society.

Grove, Curtis S., Bell. Died November 9, 1976 in Downey of heart disease, aged 64. Graduate of Regia Università di Napoli, Facoltà di Medicina e Chirurgia, 1937. Licensed in California in 1945. Dr. Grove was a member of the Los Angeles County Medical Association.

Heisler, Ivan Charles Francis, San Francisco. Died December 5, 1976 in San Francisco, aged 55. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1948. Licensed in California in 1948. Dr. Heisler was a member of the San Francisco Medical Society.

Howard, Harry P., Atherton. Died May 21, 1976 of heart disease, aged 65. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1938. Licensed in California in 1938. Dr. Howard was a member of the San Mateo County Medical Society.

Irvine, George Samuel, San Leandro. Died December 24, 1976 in Castro Valley of myocardial infarction, aged 69. Graduate of the University of Oklahoma School of Medicine, Oklahoma City, 1932. Licensed in California in 1933. Dr. Irvine was a member of the Alameda-Contra Costa Medical Association.

Johnson, Clarence E., Yountville. Died November 30, 1976 in Vacaville of heart disease, aged 68. Graduate of Wayne University College of Medicine, Detroit, 1935. Licensed in California in 1963. Dr. Johnson was a retired member of the Napa County Medical Society.

Jones, John Clifton, Los Angeles. Died December 4, 1976, aged 73. Graduate of the University of Michigan Medical School, Ann Arbor, 1929. Licensed in California in 1934. Dr. Jones was a member of the Los Angeles County Medical Association.

Kirsten, Erwyn L., Los Angeles. Died May 20, 1976 of heart disease, aged 69. Licentiate of the Royal College of Physicians of London, 1935. Licensed in California in 1936. Dr. Kirsten was a member of the Los Angeles County Medical Association.

Klein, Paul E., Hughson. Died December 28, 1976 in Hughson, aged 54. Graduate of the University of Southern California School of Medicine, Los Angeles, 1947. Licensed in California in 1947. Dr. Klein was a member of the Stanislaus County Medical Society.

Morrow, William Edward, Richmond. Died December 18, 1976 in San Pablo of cerebrovascular occlusion, aged 64. Graduate of the University of Illinois College of Medicine, 1942. Licensed in California in 1948. Dr. Morrow was a member of the Alameda-Contra Costa Medical Association.

Rosenblum, Harold H., San Francisco. Died January 1, 1977 in San Francisco, aged 71. Graduate of the University of California Medical School, Berkeley-San Francisco, 1930. Licensed in California in 1930. Dr. Rosenblum was a member of the San Francisco Medical Society.

Vollert, Edward F., San Francisco. Died December 11, 1976, aged 73. Graduate of Marquette University School of Medicine, Milwaukee, 1928. Licensed in California in 1928. Dr. Vollert was a retired member of the San Francisco Medical Society.

Woods, Charles Marshall, Danville. Died December 9, 1976 in Walnut Creek of heart disease, aged 55. Graduate of the University of Kansas School of Medicine, Lawrence-Kansas City, 1950. Licensed in California in 1951. Dr. Woods was a member of the Alameda-Contra Costa Medical Association.

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William Whiting, MD, San Francisco

9:40 **Occupational Hazards in Industry and Business**
O. Bruce Dickerson, MD, Mountain View

10:20 Break

10:45 **Legal Implications of Physical Examinations**
Jean Felton, MD, Long Beach

11:30 **Questions and Answers**

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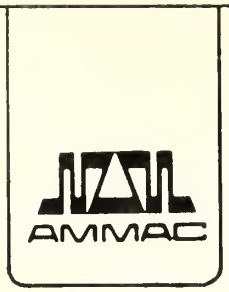

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CANCER

March 6—**Tumors of the Salivary Gland.** Calif. Tumor Tissue Registry at Disneyland Hotel, Anaheim. Sunday. 6 hrs. $100. Contact: Weldon K. Bullock, MD, Ex. Dir., Calif. Tumor Tissue Registry, 1200 N. State St., Los Angeles 90033. (213) 226-4614.

March 16-19—**Modern Concepts in Oncology—5th Annual Seminar.** UCLA at Beverly Hilton Hotel, Beverly Hills. Wednesday-Saturday.

March 19—**Cancer Screening and Cancer Control.** UCSF at Childrens Hospital, San Francisco. Saturday.

March 19—**Tumor Immunology, Clinical Applications.** San Francisco Regional Tumor Foundation at San Francisco. Saturday. Contact: Norma Schlager, PhD, S.F. Regional Tumor Foundation, 14th and Lake, San Francisco 94118. (415) 221-2132.

March 25—**Cancer of the Ovary.** California Hospital Medical Center, Los Angeles. Friday. Contact: Kenneth L. Senter, MD, Dir., Med. Ed., CHMC, 1414 S. Hope St., Los Angeles 90015. (213) 748-2411.

May 14-15—**Skin Cancer.** UCSF. Saturday-Sunday.

May 21-22—**Management of Cancer—3rd Annual Workshop.** Institute for Cancer and Blood Research and Century City Hospital Radiation Therapy Center at Riviera Country Club, Pacific Palisades. Saturday-Sunday. 16 hrs. Contact: Howard R. Bierman, MD, Sci. Dir., Institute for Cancer and Blood Research, 140 N. Robertson Blvd., Beverly Hills 90211. (213) 655-4706.

MEDICINE

February 16-18—**Recent Advances in Gastroenterology.** UCSF at Fairmont Hotel, San Francisco. Wednesday-Friday.

February 18-19—**Dermatotoxicology.** UCSF. Friday-Saturday.

February 19-26—**Noah Worchester Dermatologic Society.** Canyon Hotel, Palm Springs. One week. Contact: D. W. Whetsell, Lt. Col. USAF, MC, Soc. of Air Force Physicians, P.O. Box 3534, Malcolm Grow USAF Med. Ctr., Andrews AFB, MD 20331.

March 2-4—**Acute Respiratory Failure in Black and White—Annual Postgraduate Course.** California Thoracic Society at Sir Francis Drake Hotel, San Francisco. Wednesday-Friday. 18 hrs. $150 for members; $175, nonmembers. Contact: Ms. Elma Plappert, Exec. Sec., CTS, 424 Pendleton Way, Oakland 94621. (415) 638-5864.

March 11-12—**Clinical and Technical Application of the Intra-Aortic Balloon Pump.** See Surgery, March 11-12.

March 11-13—**American College of Physicians—Southern California Regional Meeting.** Vacation Village Hotel, San Diego. Friday-Sunday. Contact: John C. McCall, Jr., MD, 9844-400 Genesee Ave., La Jolla 92037.

March 14-16—**Advances in Cardiology.** Foundation for Cardiovascular Research and Hospital of the Good Samaritan at Riviera Hotel, Palm Springs. Monday-Wednesday. 17½ hrs. $200. Contact: Foundation for Cardiovascular Research, 10 Congress St., Suite 203, Pasadena 91105.

March 15-16—**American College of Physicians—Hawaii Regional Meeting.** Pacific Club, Honolulu. Tuesday-Wednesday. Contact: Bernard W. D. Fong, MD, 97 Dowsett Ave., Honolulu 96817.

March 17-19—**Cardiovascular Disease—1977: Practical Diagnosis and Management.** American College of Cardiology at Hotel del Coronado, Coronado. Thursday-Saturday. Contact: Mary Anne McInerny, Dir., Dept. of Cont. Ed. Prog., ACC, 9650 Rockville Pike, Bethesda, Md. 20014.

March 18—**Practical Approach to Coagulation.** PMC. Friday.

March 21-25—**Cardiac Electrophysiology.** USC at Erawan Garden Hotel, Palm Springs. Monday-Friday.

KEY TO ABBREVIATIONS AND SYMBOLS

Medical Centers and CMA Contacts for Information

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103. (415) 777-2000.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Duane Dillman, PhD, Director, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 564-5911, ext. 391.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr., MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, Ext. 2400.

PMC: Pacific Medical Center
Contact: Allen J. Enelow, MD, Chairman, Education Committee, Pacific Medical Center, P.O. Box 7999, San Francisco 94120. (415) 563-4321.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Neil C. Andrews, MD, Chairman, Department of Postgraduate Medicine, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, California College of Medicine, Irvine
Contact: Robert Combs, MD, Associate Dean, Continuing Medical Education, University of California, Irvine—California College of Medicine, Irvine 92717 (714) 833-5991.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, P.O. Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: David Allan, MD, Associate Dean for Continuing Medical Education, 1309 Basic Sciences Building, University of California, San Diego, School of Medicine, La Jolla 92037. (714) 452-3708.

UCSF: University of California, San Francisco
Contact: Malcolm S. M. Watts, MD, Associate Dean and Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 226-2047.

March 21-25—**Recent Advances in Endocrinology and Metabolism.** UCSF at Sheraton Palace, San Francisco. Monday-Friday.

March 21-April 1—**Intensive Review of Internal Medicine.** USC Two weeks.

March 24-25—**Cardiac Disease for the Practicing Physician, Diagnosis and Management 1977—3rd Annual Symposium.** Los Angeles Heart Institute at St. Vincent Medical Center, Los Angeles. Thursday-Friday. 10 hrs. $100. Contact: Irma Larsen, RN, L.A. Heart Institute, 123 S. Alvarado St., Los Angeles 90057. (213) 413-5220.

March 28-April 1—**Consultant's Course in Dermatology.** UCSF. Monday-Friday.

March 30—**Cardiac Care in Your Office.** American Heart Assn., Central Valley Chapter, at Sheraton Inn, Fresno. Wednesday. 6½ hrs. $35. Contact: Norman Sharrer, MD, 3835 N. West Ave., Fresno 93705.

April 4-13—**Cardiology for the Consultant: A Clinician's Retreat.** American College of Cardiology at Rancho Santa Fe. 10 days. Contact: Mary Ann McInerny, Dir., Dept. of Cont. Ed. Programs, ACC, 9650 Rockville Pike, Bethesda, MD 20014.

April 18-22—**Advances in Internal Medicine.** UCSF. Monday-Friday.

April 23—**Controversies in Internal Medicine.** The San Jose Hospital and Health Center, Inc., and San Jose Hospital Foundation at Marriott's Great America, Santa Clara. Saturday. 6 hrs. $25. Contact: Stanley Skillicorn, MD, Dir. of Med. Ed., The San Jose Hosp. and Health Ctr., Inc., 675 E. Santa Clara, San Jose 95112. (408) 998-3212.

April 28-30—**New Approaches to Cardiac Diagnosis.** PMC at Fairmont Hotel, San Francisco. Thursday-Saturday.

May 6-7—**Update of Immunology and Allergy.** UCSD at Hilton Hotel, San Diego. Friday-Saturday.

May 7-14—**Diagnostic and Therapeutic Skills in Internal Medicine.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 30 hrs.

May 15-18—**American Thoracic Society—Annual Scientific Meeting.** Hilton Hotel, San Francisco. Sunday-Wednesday. Contact: Mr. S. R. Iannotta, Assoc. Ex. Dir., ATS, 1740 Broadway, New York 10019. (212) 245-8000.

May 20—**American Heart Association, California Affiliate—Scientific Sessions for Physicians.** Hyatt House, San Jose. Friday. Contact: Marilyn Probst, Admin. Asst., AHA, Calif. Affiliate, 1370 Mission St., San Francisco. (415) 626-0123.

May 20—**Stomatology.** STAN. Friday. 6 hrs.

May 20-21—**Hematology.** UCSF. Friday-Saturday.

May 21—**EKG Workshop.** PMC at Miyako Hotel, San Francisco. Saturday.

May 27-29—**New Concepts in Clinical Electrocardiography.** American College of Cardiology at Century Plaza Hotel, Los Angeles. Friday-Sunday. Contact: Mary Anne McInerny, Dir., Dept. of Cont. Ed. Prog., ACC, 9650 Rockville Pike, Bethesda, MD 20014.

OBSTETRICS AND GYNECOLOGY

February 17-19—**Neonatology.** USC. Thursday-Saturday.

March 18—**Birth Defects, Genetics and the High Risk Patient.** UCD at Sacramento Inn, Sacramento. Friday.

March 18—**Diabetes in Pregnancy.** USC. Friday.

March 25-27—**Gynecological Urology.** USC at Marriott Hotel, Newport Beach. Friday-Sunday.

PEDIATRICS

February 24-26—**Clinical Problems in Pediatrics—Annual Winter Meeting.** Children's Hospital Medical Center of Northern Calif. at Sahara Tahoe Hotel, Lake Tahoe. Thursday-Saturday. Contact: Gretchen Hayes, CHMC, 51st and Grove Sts., Oakland 94609.

March 11-13—**Clinical Pediatrics.** American Academy of Pediatrics, Dist. IX, Chap. 11; Childrens Hosp., of L.A.; L.A. Pediatric Society; Childrens Hosp. of Orange County; Southwestern Pediatric Society at Riviera Hotel, Palm Springs. Friday-Sunday. 12 hrs. $100. Contact: AAP, Dist. IX, Chap. 11, P.O. Box 2134, Inglewood 90305.

March 25-26—**Aspects of Adolescent Medicine.** Ojai Valley Community Hospital; National Medical Enterprises, Inc.; Doctor's Hospital, Lakewood; Ventura Co. Academy of Family Physicians at Ojai Valley Inn and Country Club, Ojai. Friday-Saturday. 14 hrs. $20. Contact: E. William Jackson, MD, Ojai Community Hosp., 1306 Maricopa Highway, Ojai 93023. (805) 646-1401.

March 25-26—**Infectious Diseases in Children.** UCD at Sacramento Inn, Sacramento, Friday-Saturday.

March 27-31—**Radiological Approach to Pediatric Problems.** See Radiology, March 27-31.

April 4-6—**American Association of Pediatric Ophthalmology.** PMC at Holiday Inn, Union Square, San Francisco. Monday-Wednesday.

April 15-16—**Aches, Pain and Dramatic Diseases in Children and Young Adults.** USC at Children's Hospital, Los Angeles. Friday-Saturday.

May 2-6—**Pediatric Review.** USC. Monday-Friday.

May 5-7—**Care of the Sick Newborn.** Memorial Hospital Medical Center, Long Beach. Thursday-Saturday. Contact: Houchang D. Modanlou, MD, 2801 Atlantic Ave., Long Beach 90801.

May 12-14—**Advances in Pediatrics.** UCSF. Thursday-Saturday.

PSYCHIATRY

April 2—**Evaluation and Management of Dangerous Behavior.** UCD at Sacramento Host, Sacramento. Saturday.

May 15-18—**New Therapeutic Approaches with Biofeedback.** UCLA at Biltmore Hotel, Santa Barbara. Sunday-Wednesday.

May 19-22—**Clinical Hypnosis—Introductory and Advanced Course.** See Of Interest To All, May 19-22.

RADIOLOGY AND PATHOLOGY

February 19-20—**Computerized Scanning of Body and Head—10th Annual Leo G. Rigler Radiology Seminar.** UCLA at Beverly Hilton Hotel, Beverly Hills. Saturday-Sunday.

March 5-6—**Diagnostic Nuclear Imaging.** UCSF at Fairmont Hotel, San Francisco. Saturday-Sunday.

March 7-11—**Diagnostic Radiology 1977.** UCSF at Fairmont Hotel, San Francisco. Monday-Friday.

March 12-13—**A Practical Course in Ultrasound.** UCSF at Fairmont Hotel, San Francisco. Saturday-Sunday.

March 17-19—**Annual Western-International CT Scanning Symposium.** Memorial Hospital Medical Center, Long Beach. Thursday-Saturday. 15 hrs. $200. Contact: Margaret Frederick, Center for Health Education, Memorial Hosp. Med. Ctr., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3823.

March 27-31—**Radiological Approach to Pediatric Problems.** USC at Bonaventure Hotel, Los Angeles. Sunday-Thursday.

April 29-30—**Sierra Valley Nuclear Medicine Association—Annual Symposium.** Sahara Tahoe Hotel, South Lake Tahoe. Friday-Saturday. Contact: Martha Frazer, Mercy San Juan Hospital, Dept. of Nuclear Medicine, 6501 Coyle Ave., Carmichael 95608.

May 14—**Radiological Evaluation of the Liver, Pancreas and Biliary Tract.** UCD at Woodlake Inn, Sacramento. Saturday.

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SURGERY AND ANESTHESIOLOGY

February 22-March 1—**Ventilatory and Circulatory Care of the Seriously Ill Patient.** Calif. Society of Anesthesiologists at Oahu and Kauai, Hawaii. One week. $125. Contact: Norm Catron, CSA, 100 S. Ellsworth St., San Mateo 94401. (415) 348-1407.

February 23-25—**Anterior Segment Disease in Surgery.** USC. 21 hrs. Wednesday-Friday.

February 23-27—**Controversial Areas in Surgery of the Head and Neck.** UCSD at Vacation Village Hotel, San Diego. Wednesday-Sunday. Contact: Alan M. Nahum, MD, 225 W. Dickinson St., San Diego 92103. (714) 294-5910.

February 25-26—**Retina Workshop.** Retina Research Fund of St. Mary's Hospital and Medical Center at Hyatt on Union Square, San Francisco. Friday-Saturday. 12 hrs. $135. Contact: Ms. Claire Ohiyon, c/o Howard Schatz, MD, 3637 Sacramento St., San Francisco 94118. (415) 921-4860.

March 2-4—**Acute Respiratory Failure in Black and White.** See Medicine, March 2-4.

March 3-4—**Oculoplastic Surgery.** UCSF. Thursday-Friday.

March 3-7—**Controversial Areas in Surgery—14th Annual Seminar.** UCLA at Palm Springs. Thursday-Monday.

March 7-11—**Surgical Forum.** Society of Graduate Surgeons of the Los Angeles County Hospital at Ambassador Hotel, Los Angeles. Monday-Friday. Contact: Miss Dee Davis, Exec. Sec. L.A. Obstetrical and Gynecological Society, 5410 Wilshire Blvd., Los Angeles 90036. (213) 937-5514.

March 8-12—**Vascular Surgery—5th Annual Symposium.** UCLA at Palm Springs. Tuesday-Saturday.

March 11-12—**Ophthalmology Update I.** PMC at Golden Gateway Holiday Inn, San Francisco. Friday-Saturday.

March 11-12—**Retinal Disease.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Friday-Saturday. 12 hrs. $125. Contact: Margaret Frederick, Exec. Sec., Center for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3823.

March 11-12—**Symposium on Clinical and Technical Application of the Intra-Aortic Balloon Pump.** Daniel Freeman Hospital at Airport Park Hotel, Inglewood. Friday-Saturday. $100. Contact: Josephine Maxwell, Dept. of Education, Daniel Freeman Hospital, 333 N. Prairie Ave., Inglewood 90301. (213) 674-7050, ext 112.

March 13-17—**American Urological Association, Western Section.** Fairmont Hotel, San Francisco. Sunday-Thursday. 25 hrs. $170 for members; $195, nonmembers. Contact: Frank J. DeSantis, Exec. Sec., 21510 S. Main St., Carson 92037. (213) 549-3470.

March 14-18—**Anesthesiology 1977.** Anesthesiology Educational Foundation at Mammoth Lakes. Monday-Friday. Contact: Ronald L. Katz, MD, Dept. of Anesthesiology, UCLA School of Medicine, Los Angeles 90024.

March 17-19—**Plastic Ophthalmic Surgery: Intraocular Lenses Insertion.** St. Mary's Hospital and Medical Center, San Francisco. Thursday-Saturday. 24 hrs. $250. Contact: J. A. Sarrail, MD, 450 Sutter St, San Francisco. (415) 397-1500.

March 25-26—**Retina Workshop.** Retina Research Fund of St. Mary's Hospital and Medical Center at Hyatt on Union Square, San Francisco. Friday-Saturday. 12 hrs. $135. Contact: Ms. Claire Ohiyon, c/o Howard Schatz, MD, 3637 Sacramento St., San Francisco 94118. (415) 921-4860.

March 25-27—**Gynecological Urology.** See Obstetrics and Gynecology, March 25-27.

March 28-31—**American College of Surgeons—5th Annual Spring Meeting.** Bonaventure Hotel, Los Angeles. Monday-Thursday. Contact: Edwin W. Gerrish, MD, Asst. Dir., Assembly, ACS, 55 E. Erie St., Chicago 60611. (312) 664-4050.

March 31-April 1—**Diseases of the Urinary Tract.** STAN at Rickey's Hyatt House, Palo Alto. Thursday-Friday. 16 hrs. $150.

April 1-3—**Management of Trauma.** UCSD at Sheraton Harbor Island Hotel, San Diego. Friday-Sunday. $175. Contact: Nomi Feldman, Box 705, La Jolla 92038.

April 4-6—**American Association of Pediatric Ophthalmology.** See Pediatrics, April 4-6.

April 7-9—**Orbital Surgery.** UCLA. Thursday-Saturday.

April 14-15—**Office Orthopedics.** See Of Interest To All, April 14-15.

April 15-16—**Hand Injuries and Infections.** PMC. Friday-Saturday.

April 21-22—**Diagnosis and Clinical Management of Glaucoma.** Jules Stein Eye Institute at Century Plaza Hotel, Los Angeles. Thursday-Friday. Contact: Jules Stein Eye Institute, UCLA School of Medicine, Los Angeles 90024.

April 21-22—**Phaco-Fragmentation.** UCSF. Thursday-Friday.

April 21-23—**General Surgery—Annual Course.** Thursday-Saturday.

April 23—**Audiology for Practicing Physicians.** PMC. Saturday.

April 28-29—**Current Problems in Intensive Care: Mechanical Ventilation.** UCSF at Stanford Court Hotel, San Francisco. Thursday-Friday. $125.

April 28-30—**Retina Workshop.** Retina Research Fund of St. Mary's Hospital and Medical Center, San Francisco, at Silverado, Napa Valley. Thursday-Saturday. 12 hrs. $135. Contact: Ms. Claire Ohiyon, c/o Howard Schatz, MD, 3637 Sacramento St., San Francisco 94118. (415) 921-4860.

April 30—**Flexible Bronchofibroscopy.** PMC. Saturday.

April 30-May 7—**Management of the Surgical Patient.** STAN at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week $275.

May 19-20—**Phaco-Fragmentation.** UCSF. Thursday-Friday.

May 19-21—**Neurosurgery—7th Annual Course.** UCSF at Hyatt on Union Square, San Francisco. Thursday-Saturday.

May 26-28—**Retina Workshop.** Retina Research Fund of St. Mary's Hospital and Medical Center, San Francisco, at Quail Lodge, Carmel Valley. Thursday-Saturday. 12 hrs. $135. Contact: Ms. Claire Ohiyon, c/o Howard Schatz, MD, 3637 Sacramento St., San Francisco 94118. (415) 921-4860.

Orthopaedic Audio-Synopsis Foundation. A non-profit service for Orthopaedic Surgeons publishing monthly recorded teaching programs which include summaries of pertinent literature and excerpts from national and international orthopaedic meetings. Monthly c-60 cassette tapes. Annual subscription rate $75 ($37.50 for residents). Contact: A. Harris, Man. Ed., OASF, 1510 Oxley St., So. Pasadena 91030. (213) 682-1760.

OF INTEREST TO ALL PHYSICIANS

February 16—**Diagnostic Horizons 1977—15th Annual Symposium.** Eden Hospital at Willow Park Restaurant, Castro Valley. Wednesday. $35. Contact: E. Gregory Thomas, MD, Eden Hospital, 20103 Lake Chabot Rd., Castro Valley 94546. (415) 537-1234, ext. 213.

February 20-25—**Advances in Patient Care—4th Annual Conference.** Medical Communications and Services Assn. at Maui Surf Hotel, Maui, Hawaii. Sunday-Friday. 24 hrs. $175. Con-

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tact: Spring Zoog, Conf. Coordinator, MCSA, 315 U-District Bldg., 1107 N.E. 45th St., Seattle 98105. (206) 633-0505.

February 22-26—**Sports Medicine—Ski Injuries.** UCSF at Lake Tahoe. Tuesday-Saturday.

February 26—**Workshop for Physicians and Health Professionals.** UCLA. Saturday.

February 26—**Understanding the Histanic Patient.** PMC at University of San Francisco. Saturday.

February 28-March 4—**Basic Science for Clinicians.** STAN. Monday-Friday. $250.

March 4—**Diabetes Program—4th Annual.** UCD at Red Lion Motor Inn, Sacramento. Friday.

March 4-9—**California Medical Association—106th Annual Session.** Disneyland Hotel, Anaheim. Friday-Wednesday. Contact: Gail Jara, CMA.

March 8-12—**Sports Medicine for the Primary Physician.** Univ. of Hawaii School of Medicine and American Academy of Family Physicians at Princess Kaiulani Hotel, Honolulu. Tuesday-Saturday. 18 hrs. $200. Contact: Mr. Harold Brown, Hawaii Conferences Services, P.O. Box 22670, Honolulu 96822.

March 13-17—**Association for the Advancement of Medical Instrumentation—12th Annual Meeting.** Hyatt Regency Hotel, San Francisco. Sunday-Thursday. Contact: Michael J. Miller, Exec. Dir., AAMI, 1901 N. Ft. Myer Dr., Suite 602, Arlington, Va. 22209. (703) 525-4890.

March 16-April 16—**Family Medicine Tutorial.** DREW. Wednesday mornings.

March 18-24—**LLU School of Medicine—Annual Postgraduate Convention.** Friday-Thursday. Contact: Alumni Association, LLU.

March 21-25—**Postgraduate Institute for Emergency Physicians, Symposium II.** UCSD. Monday-Friday.

March 26—**Prevention of Athletic Injuries.** Sonoma County Medical Assn. at Calif. State College, Sonoma, Rohnert Park. Saturday. Contact: William E. Tewksbury, Asst. Exec. Dir., SCMA, 3452 Mendocino Ave., Santa Rosa 95401. (707) 544-2010.

March 26-27—**Practical Endocrinology for the Primary Care Physician.** UCLA. Saturday-Sunday. 12 hrs. $125.

March 28-April 1—**Therapy: Principles and Use of Drugs.** STAN. Monday-Friday.

April 1-2—**Providence Hospital—Annual Spring Seminar.** Providence Hospital, Oakland. Friday-Saturday. 9 hrs. Contact: Nancy Hansen, Coord., Med. Staff, Providence Hospital, Box 23020, Oakland 94623. (415) 835-4500, ext 373.

April 1-2—**West Coast Counties Postgraduate Institute.** CMA at Quail Lodge, Carmel. Friday-Saturday.

April 2—**Total Parenteral Nutrition.** PMC. Saturday.

April 13-14—**American Geriatrics Society—34th Annual Meeting.** Fairmont Hotel, San Francisco. Wednesday-Thursday. Contact: Marcia Roye, Assoc. Exec. Dir., AGS, 10 Columbus Cir., New York 10019. (212) 582-1333.

April 14-15—**Office Orthopedics.** USC. Thursday-Friday.

April 15-16—**Aches, Pain and Dramatic Diseases in Children and Young Adults.** See Pediatrics, April 15-16.

April 15-16—**Practical ENT for Primary Physicians.** UCSF. Friday-Saturday.

April 16-23—**Emergency Medicine.** USC at Kona Surf Hotel, Kona, Hawaii. One week.

April 18-October 25—**Intensive Review of Family Practice.** USC. Thursday evenings.

April 22-24—**Family Medicine Intensive Review.** DREW. Friday-Sunday.

April 23—**Audiology for Practicing Physicians.** See Surgery, April 23.

April 28-29—**Current Problems in Intensive Care.** UCSF at Stanford Court, San Francisco. Thursday-Friday.

April 29—**Continuing Medical Education Seminar—6th Annual.** LLU at Bakersfield. Friday.

April 29-30—**San Joaquin Valley Counties Postgraduate Institute.** CMA at Ahwahnee Hotel, Yosemite. Friday-Saturday.

May 7—**Current Concepts in Drug Therapy—8th Annual Symposium on Clinical Pharmacology.** STAN at Palo Alto Medical Clinic, Palo Alto. Saturday. Contact: Stanley Cohen, MD, Clinical Pharm., Dept. of Medicine, Stanford Univ. Sch. of Med., Stanford 94305. (415) 497-5315.

May 7-8—**Summer Emergencies.** Dept. of Emergency Medicine, Valley Medical Center, Fresno; San Joaquin Valley Area Health Education Center at Holiday Inn, Monterey. Saturday-Sunday. $80, physicians; $40, residents, students, nurses. Contact: Frank Mannix, MD, Dept. of Emergency Med., Valley Med. Ctr., 445 S. Cedar, Fresno 93702.

May 9-13—**Topics in Emergency Medicine.** UCSF at Franklin Hospital, San Francisco. Monday-Friday.

May 16-20—**Postgraduate Institute for Emergency Physicians, Symposium I.** UCSD at Sheraton Harbor Island Hotel, San Diego. Monday-Friday.

May 16-22—**Diving Medicine.** UCSF at VA Hospital, Fresno. Monday-Sunday.

May 19-22—**Clinical Hypnosis—Introductory and Advanced Course.** American Society of Clinical Hypnosis at San Francisco. Thursday-Sunday. 25 hrs. $225. Contact: William F. Hoffman, Jr., Exec. Sec., ASCH, Education and Research Foundation, 2400 E Devon Ave., Suite 218, Des Plaines, ILL 60018. (312) 297-3317.

May 22-27—**Fingers-to-the-Toes—An Orthopedic Approach for the General Practitioner.** UCD at Stanford Sierra Camp, Fallen Leaf Lake. Sunday-Friday.

May 26-30—**Patient Oriented Applied Medical Advances.** UCSF at Hawaii. Thursday-Monday.

Audio-Digest Foundation. A non-profit subsidiary of CMA. Twice-a-month tape recorded summaries of leading national meetings and surveys of current literature. Services by subscription in: Family Practice, Surgery, Internal Medicine, Ob/Gyn, Pediatrics, Psychiatry, Anesthesiology, Ophthalmology, Otorhinolaryngology. Catalog of lectures and panel discussions in all areas of medical practice also available. $90 per year. Also available are ACOG Audio Education Courses, edited and produced by Audio-Digest Foundation —32, 6- and 3-hour cassette courses available including: Family Life and Sexual Counseling; Medical Complications of Pregnancy; Gynecological Endocrinology; Psychosomatic Ob/Gyn; Immunology in Ob/Gyn; and Pediatric and Adolescent Gyn. Available soon: Cassette albums of State of the Art Lectures and Workshops from 1976 American College of Physicians meeting and Postgraduate Courses from 1976 American Psychiatric Association meeting. Contact: Mr. Claron L. Oakley, Editor, Suite 700, 1930 Wilshire Blvd., Los Angeles 90057. (213) 483-3451.

PRECEPTORSHIPS AND TRAINEESHIPS

Training for Physicians in General Internal Medicine. LLU. Four weeks or more, by arrangement. Bedside and classroom training, practical aspects of clinical care and management. 160 hrs. Contact: John E. Peterson, MD, LLU.

Training of Physicians in Modern Concepts of Pulmonary Care. LLU. Four weeks or more, by arrangement. Diagnostic and therapeutic methods in medical chest disease, physiological methodology of modern pulmonary care programs, use of new instrumentation in the field. 160 hrs. Contact: John E. Hodgkin, MD, Chief, Section of Medical Chest Diseases, LLU.

Physician-in-Residence Preceptorship in Pulmonary Disease. USC, Pulmonary Disease Section, Dept. of Medicine and Postgraduate Medical Education. One month or more, by arrangement. Opportunity for practicing physician to achieve specified knowledge and skills in adult pulmonary medicine. Contact: Oscar J. Balchum, MD, PhD, USC.

Training for Physicians in Nephrology. LLU. Four weeks or more, by arrangement. Hemodialysis, peritoneal dialysis, renal biopsy, and kidney transplantation. 160 hrs. Contact: Robert E. Soderblom, MD, LLU.

Preceptorships in Cardiology. PMC. By arrangement. $200 per mo.; $500 for 3 mos. Contact: Arthur Selzer, MD, PMC.

Preceptorships in Practical Office Dermatology. PMC. Wednesdays or Fridays, 9:00 a.m.-12:00 noon, for 10 weeks. Periods begin Oct., Jan., or April. $100. Contact: Harold M. Schneidman, MD, Dept. of Dermatology, PMC.

Preceptorships in Infectious Disease. PMC. Full time for four weeks. To be arranged. $250. Contact: Rodney J. Valentine, MD, Chief, Div. of Infectious Diseases, PMC.

Preceptorships in Basic Sciences, Biochemistry and Biophysics, Dermatology, Echocardiography, International Health, Microbiology, Neurological Surgery, Obstetrics and Gynecology, Pediatrics, Pharmacology and Experimental Therapeutics, Physiology, Psychiatry, Urology. UCSF. By special arrangement.

Traineeships in Renal Dialysis. UCSF. By special arrangement.

OREGON

COUNCIL ON MEDICAL EDUCATION

THIS BULLETIN of information regarding continuing education programs and meetings of various medical organizations in Oregon is supplied by the Council on Medical Education of the Oregon Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Council on Medical Education, Oregon Medical Association, 5210 S.W. Corbett Ave., Portland, OR 97201; or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

University of Oregon Medical School, Department of Internal Medicine, 3181 SW Sam Jackson Park Road, Portland 97201:

Every Tuesday, 8:00 a.m. to 9:00 a.m.—**Internal Medicine Grand Rounds.** Library Auditorium, University of Oregon Health Sciences Center, Portland. Contact: Stephen R. Jones, MD, Department of Internal Medicine, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, 97201.

Providence Medical Center, 700 NE 47th Avenue, Portland 97213:

Every Wednesday, 8:00 a.m. in the auditorium—**Spring Medical Grand Rounds,** Providence Medical Center. Contact: David N. Gilbert, MD, Director of Medical Education, Providence Medical Center, 700 NE 47th, Portland 97213.

FAMILY PRACTICE

Every Wednesday, 11:00 a.m. to 12:00 Noon. **Family Practice Grand Rounds.** Family Practice Center, University of Oregon Health Sciences Center. Contact: William A. Fisher, MD, University of Oregon Health Sciences Center, Department of Family Practice, 3181 SW Sam Jackson Park Road, Portland 97201.

February 14-18—**Family Practice Review.** Sheraton Hotel, Lloyd Center, Portland. Contact: William A. Fisher, MD, Department of Family Practice, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland 97201.

May 5-8—**Oregon Academy of Family Physicians 30th Annual Scientific Assembly.** Salishan Lodge, Gleneden Beach. Contact: Skippie Patterson, Executive Secretary, Oregon Academy of Family Physicians, 2188 SW Main, Portland 97205.

INTERNAL MEDICINE

Every Tuesday, 8:00 a.m. to 9:00 a.m.—**Internal Medicine Grand Rounds.** Library Auditorium, University of Oregon Health Sciences Center, Portland. Contact: Stephen Jones, MD, Department of Internal Medicine, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland 97201.

OF INTEREST TO ALL PHYSICIANS

February 17-19—**Oregon Thoracic Society Annual Chest Disease Conference.** Salishan Lodge, Gleneden Beach, Oregon. Contact: Max R. Mehlhaff, Executive Secretary, Oregon Thoracic Society, 1020 SW Taylor St., Portland 97205.

March 3-4—**Postgraduate Course on Advances in Rheumatology.** Sheraton Hotel, Portland. Contact: R. E. Rinehart, MD, Oregon Arthritis Foundation, PO Box 42067, Portland 97242.

March 10—**Interdisciplinary Team Coordination in Long Term Care.** Ramada Inn, Tualatin. Contact: Janet Teaff, RN, Associate Executive Director, Oregon Nurses Association, 26 SW 5th Avenue, Portland 97204. (Program will be repeated March 11 at Umpqua Community College in Roseburg.)

March 11—**Urology Day.** Sacred Heart General Hospital, Eugene. Contact: Kenneth Blundon, MD, 132 E. Broadway, Eugene 97401.

April 13-15—**University of Oregon Health Sciences Center Annual Alumni Meeting and Sommer Memorial Lectures.** Library Auditorium, University of Oregon Health Sciences Center. Contact: Michele Wiley, Medical Relations Officer, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland 97201.

April 20—**Biofeedback in Medicine.** Withycombe Hall, Oregon State University, Corvallis. Contact: R. L. Phillips, Ads A 600 Oregon State University, Corvallis 97331.

WASHINGTON, ALASKA, MONTANA AND IDAHO

In order to have future activities listed here or to receive information on these and other activities, please write Ms. Joan M. Kelday, Information Specialist, Continuing Medical Education, WAMI Program, University of Washington School of Medicine, Health Sciences Building, SC-64, Seattle, Washington 98195. Phone: (206) 543-6995.

February 15-18—**Gastrointestinal Disease.** Tuesday-Friday. 8-10 a.m., St. Joseph Hospital, Tacoma, Wash. 8 hrs. Contact: Mrs. Maxine Bailey, College of Medical Education, The University of Puget Sound, 1500 N. Warner, Tacoma, WA 98416. (206) 756-3152.

February 24-25—**Modern Concepts in Allergy.** Thursday-Friday. Virginia Mason Medical Center Auditorium, Seattle. 11½ hrs. $75. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) 223-6898.

February 24-25—**Atherosclerosis.** Thursday-Friday. Seattle. Location, hours, fee to be determined. Contact: Pat Lind, Div. of CME, HSB SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-9495 or 543-1050.

February 24—**Internal Medicine Review: Liver and Pancreatic Diseases.** Univ. of Wash. in Billings, Mont. 7-9:30 a.m., Marillac Hall, 2½ hrs. Contact: Mrs. Frances Burt, Cont. Med. Ed. Marillac Hall, Billings, MT 59101. (406) 252-2121, Ext. 258.

February 25—**Internal Medicine Review: Liver and Pancreatic Diseases.** Univ. of Wash. in Missoula, Mont. 8:30-11 a.m., St. Patrick Hospital. 2½ hrs. Contact James E. Gouaux, MD, 515 Kensington, Missoula, MT 59801. (406) 549-4581.

February 28-March 1—**Emergency Medicine.** Monday-Friday. Seattle. Location, hours, fee to be determined. Contact: Pat Lind, Div. of CME, HSB SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-9495 or 543-1050.

February 28—**Internal Medicine Review: Ophthalmology for Internists.** Monday. Univ. of Wash. in Wenatchee, Wash. 7:30-9:30 p.m., Wenatchee Valley Clinic. 2 hrs. Contact: William M. McKee, MD, PO Box 489, Wenatchee, WA 98801. (509) 663-8711.

March 1—**Internal Medicine Review: Ophthalmology for Internists.** Tuesday. Univ. of Wash. in Yakima, Wash. 5-7 p.m., Memorial Hospital. 2 hrs. Contact: Harry R. Kimball, MD, Yakima Medical Center, WA 98902. (502) 248-6791.

March 4-5—**Hematology Seminar.** Friday-Saturday. Big Sky, Mont. Contact: D. Frank Johnson, MD, Marillac Hall, Billings, MT 59101. (406) 252-2121, Ext. 258.

March 9-10—**University of Washington School of Medicine Circuit Course on Pain.** March 9, Bremerton, Wash.; March 10, Everett, Wash. 4 hrs. Physicians, $25; others, $15. Contact: Pat Lind, Div. of CME, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-9495 or 543-1050.

March 11—**Cardiovascular Orientation.** Friday. Tacoma General Hospital, Tacoma, Wash. 3 hrs. Contact: Mrs. Maxine Bailey, College of Medical Education, The University of

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Puget Sound, 1500 N. Warner, Tacoma, WA 98416. (206) 756-3152.

March 12—**Depression and Insomnia.** Saturday. Seattle. Location, hours, fee to be determined. Contact: Pat Lind, Div. of CME, HSB SC-50, Univ. of Wash. School of Med., Seattle 98195. (206) 543-9495 or 543-1050.

March 12-13—**AMA Institute on Art of Negotiations.** Saturday-Sunday. Seattle. Contact: Department of Negotiations, AMA, 535 N. Dearborn St., Chicago, IL 60610.

March 16—**Surgery: Shock and Clinical Fluid Balance.** Wednesday. Univ. of Wash. in Billings, Mont. 1-3:30 p.m., Marillac Hall. 2½ hrs. Contact: Mrs. Frances Burt, Cont. Med. Ed., Marillac Hall, Billings, MT 59101. (406) 252-2121, Ext. 258.

March 16—**Metabolic Disorders in Pediatrics.** Wednesday. Univ. of Wash. in Ancortes, Wash. 7:30-10 a.m., Island Hospital, 2½ hrs. Contact: Harry Eiesland, MD, 24th and M Ave., Ancortes, WA 98221. (206) 292-3101.

March 17-18—**What's New in Internal Medicine.** Thursday-Friday. St. Joseph Hospital, Tacoma, Wash. 12 hrs. Contact: Mrs. Maxine Bailey, College of Medical Education, The University of Puget Sound, 1500 N. Warner, Tacoma, WA 98416. (206) 756-3152.

March 18-19—**Electromyography.** Friday-Saturday. Seattle. Contact: Pat Lind, Div. of CME, HSB SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-9495 or 543-1050.

March 18-19—**Otolaryngologic and Head and Neck Emergencies.** Friday-Saturday. Virginia Mason Medical Center Auditorium, Seattle. Hours and fee to be determined. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) 223-6898.

March 21-25—**Advances in Family Practice.** Monday-Friday. Health Sciences Bldg., Seattle. Contact: Pat Lind, Div. of CME, HSB SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-9495 or 543-1050.

March 24—**Internal Medicine Review: Lower Intestinal Diseases.** Thursday. Univ. of Wash. in Billings, Mont. 7-9:30 a.m., Marillac Hall. 2½ hrs. Contact: Mrs. Frances Burt, Cont. Med. Ed., Marillac Hall, Billings, MT 59101. (406) 252-2121, Ext. 258.

March 25—**Internal Medicine Review: Lower Intestinal Diseases.** Friday. Univ. of Wash. in Missoula, Mont. 8:30-11 a.m., St. Patrick Hospital, 2½ hrs. Contact: James E. Gouaux, MD, 515 Kensington, Missoula, MT 59801. (406) 549-4581.

March 26—**Day of Pediatrics.** Saturday. Mary Bridge Children's Hospital, Tacoma, Wash. 6 hrs. Contact: Mrs. Maxine Bailey, College of Medical Education, The University of Puget Sound, 1500 N. Warner, Tacoma, WA 98416. (206) 756-3152.

March 28—**Internal Medicine Review: Immunologic Renal Disease.** Monday. Univ. of Wash. in Wenatchee, Wash. 7-9 p.m., Wenatchee Valley Clinic. 2 hrs. Contact: William M. McKee, MD, PO Box 489, Wenatchee, WA 98801. (509) 663-8711.

March 29—**Internal Medicine Review: Immunologic Renal Disease.** Tuesday. Univ. of Wash. in Yakima, Wash. 5-7 p.m., Memorial Hospital. 2 hrs. Contact: Harry Kimball, MD, Yakima Medical Center, Yakima, WA 98902. (509) 248-6791.

March 30-April 1—**30th National Conference on Rural Health.** Wednesday-Thursday. Washington Plaza Hotel, Seattle. Contact: Department of Rural and Community Health, AMA, 535 N. Dearborn St., Chicago, IL 60610.

April 1-2—**Oral-Facial Pain.** Friday-Saturday. Seattle. Contact: Pat Lind, Div. of CME, HSB SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-9495 or 543-1050.

April 6, 13, 20—**Tacoma General Topics.** Wednesdays. Tacoma General Hospital, Tacoma, Wash. 7:30-9:30 a.m. 6 hrs. Contact: Mrs. Maxine Bailey, College of Medical Education, The University of Puget Sound, 1500 N. Warner, Tacoma, WA 98416. (206) 756-3152.

April 14-15—**Respiratory Care.** Thursday-Friday. Seattle. Contact: Pat Lind, Div. of CME, HSB SC-50, Univ. of Wash. Sch. of Med., Seattle, WA 98195. (206) 543-9495 or 543-1050.

April 14-17—**Society for Obstetric Anesthesias and Perinatology.** Thursday-Saturday. Edgewater Inn, Seattle. Contact: D. H. Ralston, MD, Department of Anesthesiology, RN-10, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-4172.

April 15-16—**Nutrition for Physicians.** Friday-Saturday. Seattle. Contact: Pat Lind, Div. of CME, HSB SC-50, Univ. of Wash. Sch. of Med., Seattle, WA 98195. (206) 543-9495 or 543-1050.

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The ultimate objective test: sleep laboratory proof of effectiveness ... now in geriatric insomnia patients

Six female insomniacs, ranging in age from 67 to 82 years received Dalmane (flurazepam HCl) for seven consecutive nights in the sleep research laboratory.[1] Improvement over pre treatment baseline levels was significant for sleep induction and sleep maintenance ($p < .05$). And the greater the sleep problem in these patients, the better the effect with Dalmane (significant correlation at $p < .01$ level)

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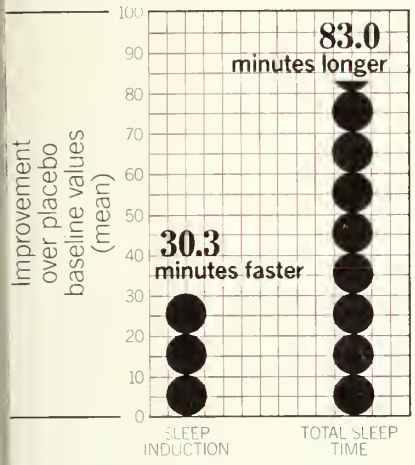

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Indications: Effective in all types of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings and/or early morning awakening; in patients with recurring insomnia or poor sleeping habits; in acute or chronic medical situations requiring restful sleep. Since insomnia is often transient and intermittent, prolonged administration is generally not necessary or recommended.
Contraindications: Known hypersensitivity to flurazepam HCl.
Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. Caution against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving).
***Usage in Pregnancy:* Several studies of minor tranquilizers (chlordiazepoxide, diazepam, and meprobamate) suggest increased risk of congenital malformations during the first trimester of pregnancy. Dalmane, a benzodiazepine, has not been studied adequately to determine whether it may be associated with such an increased risk. Because use of these drugs is rarely a matter of urgency, their use during this period should almost always be avoided. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**
Not recommended for use in persons under 15 years of age. Though physical and psychological dependence have not been reported on recommended doses, use caution in administering to addiction-prone individuals or those who might increase dosage.
Precautions: In elderly and debilitated, limit initial dosage to 15 mg to preclude oversedation, dizziness and/or ataxia. Consider potential additive effects with other hypnotics or CNS depressants. Employ usual precautions in patients who are severely depressed, or with latent depression or suicidal tendencies. Periodic blood counts and liver and kidney function tests are advised during repeated therapy. Observe usual precautions in presence of impaired renal or hepatic function.
Adverse Reactions: Dizziness, drowsiness, lightheadedness, staggering, ataxia and falling have occurred, particularly in elderly or debilitated patients. Severe sedation, lethargy, disorientation and coma, probably indicative of drug intolerance or overdosage, have been reported. Also reported: headache, heartburn, upset stomach, nausea, vomiting, diarrhea, constipation, GI pain, nervousness, talkativeness, apprehension, irritability, weakness, palpitations, chest pains, body and joint pains and GU complaints. There have also been rare occurrences of leukopenia, granulocytopenia, sweating, flushes, difficulty in focusing, blurred vision, burning eyes, faintness, hypotension, shortness of breath, pruritus, skin rash, dry mouth, bitter taste, excessive salivation, anorexia, euphoria, depression, slurred speech, confusion, restlessness, hallucinations, paradoxical reactions, *e.g.*, excitement, stimulation and hyperactivity, and elevated SGOT, SGPT, total and direct bilirubins and alkaline phosphatase.
Dosage: Individualize for maximum beneficial effect. *Adults:* 30 mg usual dosage; 15 mg may suffice in some patients. *Elderly or debilitated patients:* 15 mg initially until response is determined.
Supplied: Capsules containing 15 mg or 30 mg flurazepam HCl.

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REFERENCES:
1. Frost JD Jr: Data on file, Medical Department, Hoffmann-La Roche Inc., Nutley NJ
2. Data on file, Medical Department, Hoffmann-La Roche Inc., Nutley NJ
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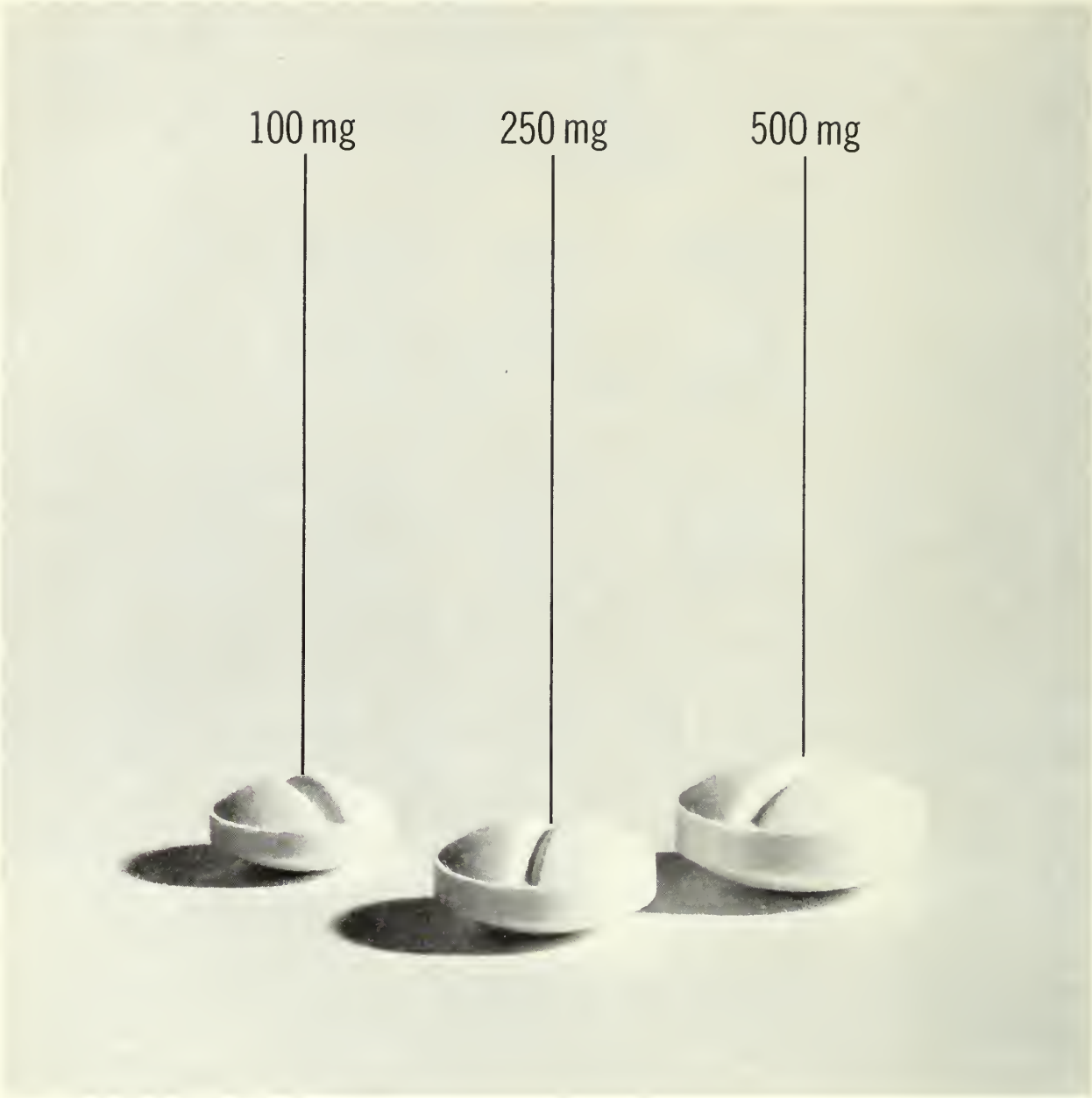

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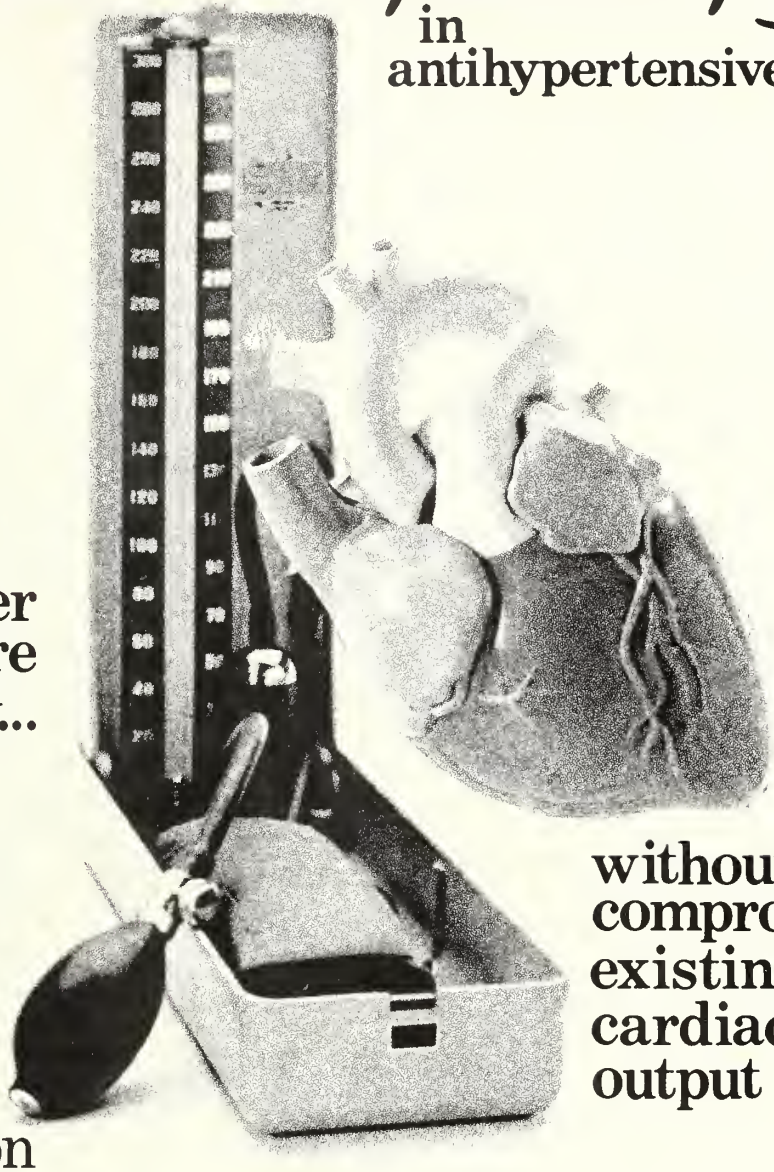

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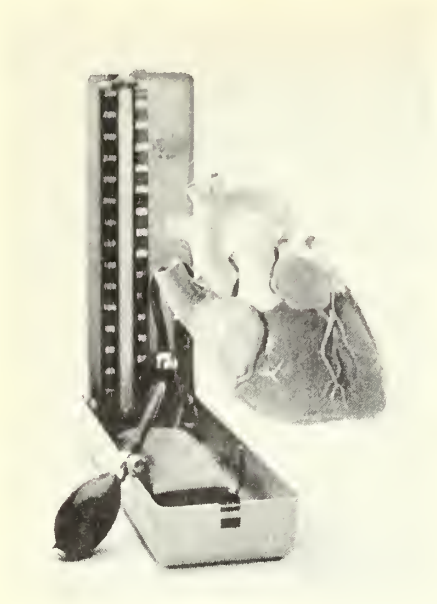

in hypertension

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Contraindications: Active hepatic disease, such as acute hepatitis and active cirrhosis; if previous methyldopa therapy has been associated with liver disorders (see Warnings); hypersensitivity

Warnings: It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed. Read this section carefully to understand these reactions.

With prolonged methyldopa therapy, 10% to 20% of patients develop a positive direct Coombs test, usually between 6 and 12 months of therapy. Lowest incidence is at daily dosage of 1 g or less. This on rare occasions may be associated with hemolytic anemia, which could lead to potentially fatal complications. One cannot predict which patients with a positive direct Coombs test may develop hemolytic anemia. Prior existence or development of a positive direct Coombs test is not in itself a contraindication to use of methyldopa. If a positive Coombs test develops during methyldopa therapy, determine whether hemolytic anemia exists and whether the positive Coombs test may be a problem. For example, in addition to a positive direct Coombs test there is less often a positive indirect Coombs test which may interfere with cross matching of blood.

At the start of methyldopa therapy, it is desirable to do a blood count (hematocrit, hemoglobin, or red cell count) for a baseline or to establish whether there is anemia. Periodic blood counts should be done during therapy to detect hemolytic anemia. It may be useful to do a direct Coombs test before therapy and at 6 and 12 months after the start of therapy. If Coombs-positive hemolytic anemia occurs, the cause may be methyldopa and the drug should be discontinued. Usually the anemia remits promptly. If not, corticosteroids may be given and other causes of anemia should be considered. If the hemolytic anemia is related to methyldopa, the drug should not be reinstituted. When methyldopa causes Coombs positivity alone or with hemolytic anemia, the red cell is usually coated with gamma globulin of the IgG (gamma G) class only. The positive Coombs test may not revert to normal until weeks to months after methyldopa is stopped.

Should the need for transfusion arise in a patient receiving methyldopa, both a direct and an indirect Coombs test should be performed on his blood. In the absence of hemolytic anemia, usually only the direct Coombs test will be positive. A positive direct Coombs test alone will not interfere with typing or cross matching. If the indirect Coombs test is also positive, problems may arise in the major cross match and the assistance of a hematologist or transfusion expert will be needed.

Fever has occurred within first 3 weeks of therapy, sometimes with eosinophilia or abnormalities in liver function tests, such as serum alkaline phosphatase, serum transaminases (SGOT, SGPT), bilirubin, cephalin cholesterol flocculation, prothrombin time, and bromsulphalein retention. Jaundice, with or without fever, may occur, with onset usually in the first 2 to 3 months of therapy. In some patients the findings are consistent with those of cholestasis. Rarely fatal hepatic necrosis has been reported. These hepatic changes may represent hypersensitivity reactions; periodic determination of hepatic function should be done particularly during the first 6 to 12 weeks of therapy or whenever an unexplained fever occurs. If fever and abnormalities in liver function tests or jaundice appear, stop therapy with methyldopa. If caused by methyldopa, the temperature and abnormalities in liver function characteristically have reverted to normal when the drug was discontinued. Methyldopa should not be reinstituted in such patients.

Rarely, a reversible reduction of the white blood cell count with primary effect on granulocytes has been seen. Reversible thrombocytopenia has occurred rarely. When used with other antihypertensive drugs, potentiation of antihypertensive effect may occur. Patients should be followed carefully to detect side reactions or unusual manifestations of drug idiosyncrasy.

Use in Pregnancy: Use of any drug in women who are or may become pregnant requires that anticipated benefits be weighed against possible risks; possibility of fetal injury can not be excluded.

Precautions: Should be used with caution in patients with history of previous liver disease or dysfunction (see Warnings). May interfere with measurement of: uric acid by the phosphotungstate method, creatinine by the alkaline picrate method, and SGOT by colorimetric methods. Since methyldopa causes fluorescence in urine samples at the same wavelengths as catecholamines, falsely high levels of urinary catecholamines may be reported. This will interfere with the diagnosis of pheochromocytoma. It is important to recognize this phenomenon before a patient with a possible pheochromocytoma is subjected to surgery. Methyldopa is not recommended for patients with pheochromocytoma. Urine exposed to air after voiding may darken because of breakdown of methyldopa or its metabolites.

Stop drug if involuntary choreoathetotic movements occur in patients with severe bilateral cerebrovascular disease. Patients may require reduced doses of anesthetics; hypotension occurring during anesthesia usually can be controlled with vasopressors. Hypertension has recurred after dialysis in patients on methyldopa because the drug is removed by this procedure.

Adverse Reactions: *Central nervous system:* Sedation, headache, asthenia or weakness, usually early and transient; dizziness, lightheadedness, symptoms of cerebrovascular insufficiency, paresthesias, parkinsonism, Bell's palsy, decreased mental acuity, involuntary choreoathetotic movements; psychic disturbances, including nightmares and reversible mild psychoses or depression.

Cardiovascular: Bradycardia, aggravation of angina pectoris. Orthostatic hypotension (decrease daily dosage). Edema (and weight gain) usually relieved by use of a diuretic. (Discontinue methyldopa if edema progresses or signs of heart failure appear.)

Gastrointestinal: Nausea, vomiting, distention, constipation, flatus, diarrhea, mild dryness of mouth, sore or "black" tongue, pancreatitis, sialadenitis.

Hepatic: Abnormal liver function tests, jaundice, liver disorders.

Hematologic: Positive Coombs test, hemolytic anemia. Leukopenia, granulocytopenia, thrombocytopenia.

Allergic: Drug-related fever, myocarditis.

Other: Nasal stuffiness, rise in BUN, breast enlargement, gynecomastia, lactation, impotence, decreased libido, dermatologic reactions including eczema and lichenoid eruptions, mild arthralgia, myalgia.

Note: Initial adult dosage should be limited to 500 mg daily when given with antihypertensives other than thiazides. Tolerance may occur, usually between second and third month of therapy; increased dosage or adding a thiazide frequently restores effective control. Patients with impaired renal function may respond to smaller doses. Syncope in older patients may be related to increased sensitivity and advanced arteriosclerotic vascular disease; this may be avoided by lower doses.

How Supplied: Tablets, containing 125 mg methyldopa each, in bottles of 100; Tablets, containing 250 mg methyldopa each, in single-unit packages of 100 and bottles of 100 and 1000; Tablets, containing 500 mg methyldopa each, in single-unit packages of 100 and bottles of 100.

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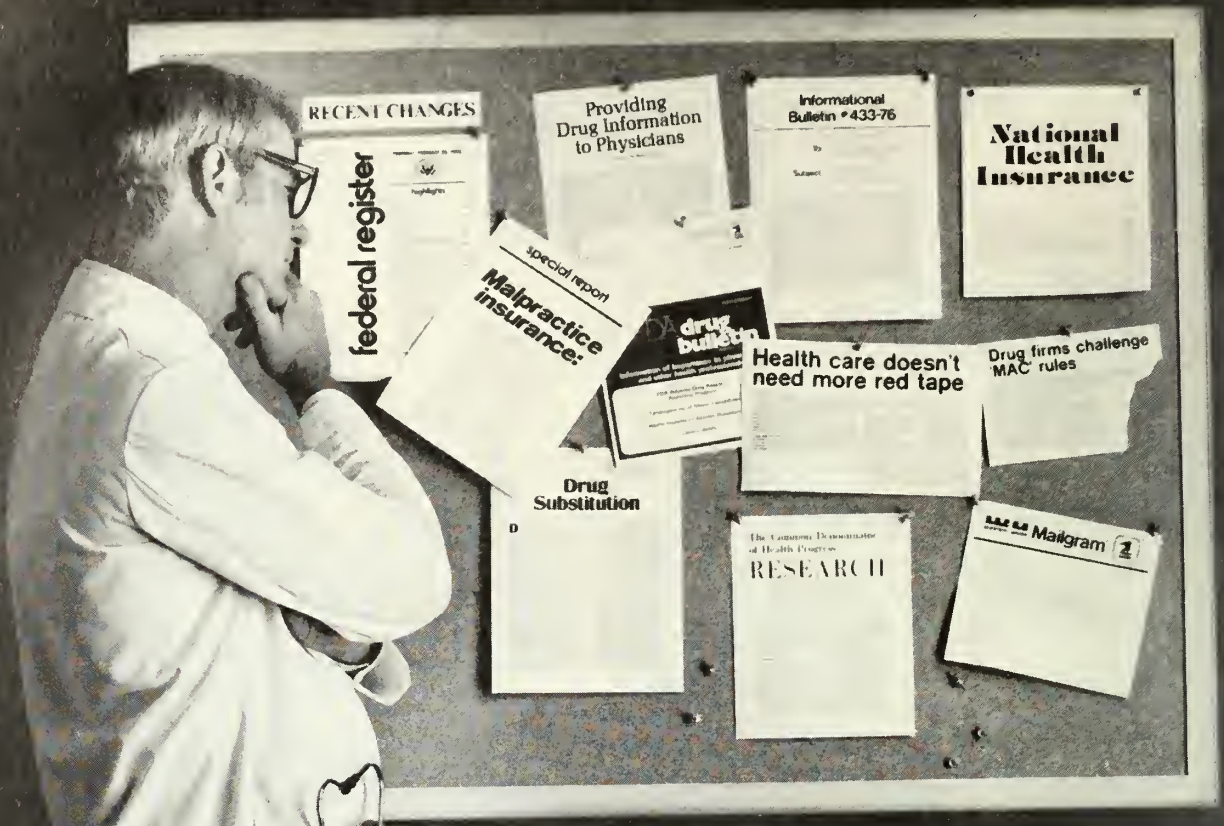
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THERE ARE A LOT OF PEOPLE GETTING BETWEEN YOU AND YOUR PATIENT.

Medicine today is in the spotlight, subjected to all kinds of scrutiny. Your control over patient therapy is being monitored, judged and occasionally abrogated, sometimes by unknown third parties.

The worry is that in the wake of this focus, the relationship between you and your patient will be weakened, without offsetting benefits. Consider three examples:

Drug substitution In most states, pharmacy laws, regulations or professional custom stipulate that your non-generic prescriptions be filled with the precise products you prescribe. But in the last five years, a dozen or more State laws have been changed, permitting the pharmacist in most cases to select a product of the same generic drug to fill any prescription.

Ironically, this dilution of physician control has taken place against a background of growing evidence that purportedly equivalent drug products may be inequivalent, since neither present drug standards nor their enforcement are optimal. In fact, the FDA itself says it has not enforced the same standards for hundreds of "follow-on" products that it had applied to the original NDA approvals. Thus physician control over patient therapy is being eroded with a risk that patients may be exposed to drugs of uncertain quality.

The major advertised claim for substitution is reduced prescription prices for consumers. Yet no documentation of any significant savings has been produced.

MAC Maximum Allowable Cost, MAC for short, is a Federal regulation designed to cut the Government's drug bill by setting price ceilings for drugs dispensed to Medicare and Medicaid patients. Unless the prescriber certifies on the prescription that a particular product is medically necessary, the Government intends to pay only for the cost of the lowest-priced, purportedly-equivalent, generally-available product. The effect of the program may be that elderly and indigent patients will be restricted to products which someone in Washington believes are priced right. Practicing doctors will have little to say about administration of the program, since Government will have absolute authority to make its choices stick.

The drug lag The future of drug and device research depends upon a scientific and regulatory environment that encourages therapeutic innovations. The American pharmaceutical industry annually is spending more than $1 billion of its own funds and evaluating more than 1,200 investigational compounds in clinical research. Disease targets include cancer, atherosclerosis, viruses and central nervous system disorders, among others. But there is a major barrier to the flow of new drugs to your patients: The cost of the research is more than ten times what it was, per product, in 1962; and whereas governmental clearance of new drug applications took six months then, it commonly consumes two years now.

The FDA needs adequate time, of course, to consider data. But it is equally clear that the present approval process contributes to needless delay of needed therapy. That's why the increased efficiency of the drug approval process is vital to all our futures.

If these issues concern you, we suggest that you make your voice heard—among your colleagues and your representatives in State legislatures and in Washington.

It could make a difference in your practice tomorrow.

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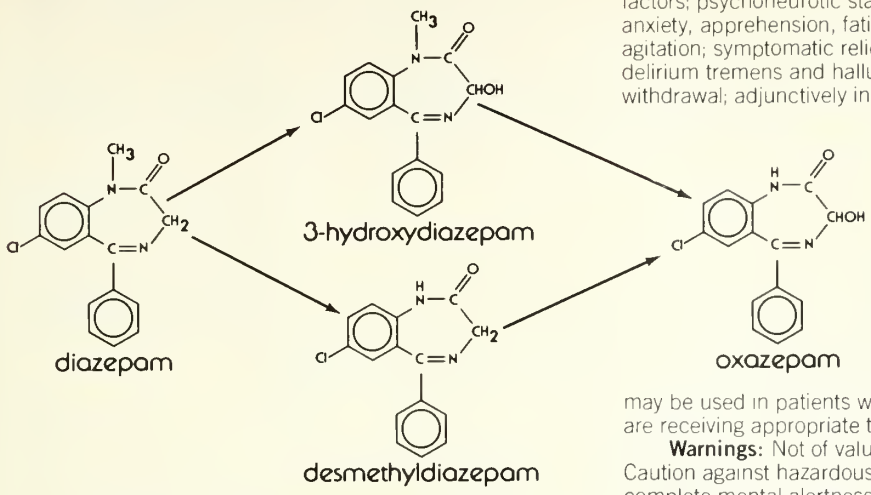

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Pharmacokinetic studies also demonstrate that Valium has a pattern of absorption, distribution, metabolism and elimination that is reliable and consistent. And, although the pharmacokinetics of a drug cannot, at present, be specifically related to its clinical effects, it is clearly a factor that distinguishes one product from another by providing important insights into how each moves through the patient's body.

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a prudent choice in psychic tension and anxiety

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Indications: Tension and anxiety states; somatic complaints which are concomitants of emotional factors; psychoneurotic states manifested by tension, anxiety, apprehension, fatigue, depressive symptoms or agitation; symptomatic relief of acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in skeletal muscle spasm due to reflex spasm to local pathology; spasticity caused by upper motor neuron disorders; athetosis; stiff-man syndrome; convulsive disorders (not for sole therapy).

Contraindicated: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms (similar to those with barbiturates and alcohol) have occurred following abrupt discontinuance (convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence.

Usage in Pregnancy: **Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Precautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed; drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.

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THE NORMAL LUNG—The Basis for Diagnosis and Treatment of Pulmonary Disease—John F. Murray, MD, Professor of Medicine and Member of the Senior Staff of the Cardiovascular Research Institute, University of California, San Francisco; Chief of Chest Division of the Medical Service, San Francisco General Hospital. W. B. Saunders Company, West Washington Square, Philadelphia (19105), 1976. 334 pages, $14.50.

A PATTERN OF HERBS—Herbs for Goodness, Food and Health and How to Identify and Grow Them. Written and illustrated by Meg Rutherford. Dolphin Books, Doubleday & Company, Inc., 245 Park Avenue, New York City (10017), 1976. 157 pages, $2.95 (Paperback).

PERINATAL MEDICINE—4th European Congress of Perinatal Medicine. Edited by Z. K. Stembera, K. Polácek and V. Sabata; Co-editors: P. M. Dunn, H.F.R. Prechtl and E. Saling. Publishing Sciences Group Inc., 162 Great Rd., Acton, MA (01720), 1975. 556 pages, $25.00.

PLAGUES AND PEOPLE—William H. McNeill, Professor of History, University of Chicago. Doubleday & Company, Inc., 245 Park Avenue, New York City (10017), 1976. 369 pages, $10.00.

THE PRETERM BABY and other Babies with Low Birth Weight—Eighth Edition—The late V. Mary Cross, OBE, MD(Lond), DPH, MMSA, DObstet, RCOG, Formerly Honorary Consultant Paediatrician, East Birmingham General Hospital, Solihull Hospital, Sorrento Maternity Hospital, Marston Green Maternity Hospital; Member of Expert Advisory Panel on Maternal and Child Health, World Health Organization, 1950-70. Revised by Eileen Elise Hill, MD, FRCP, DCH, Consultant Paediatrician, East Birmingham Hospital & Marston Green Maternity Hospital. Churchill Livingstone Medical Division, Longman, Inc., 19 West 44th St., New York City (10036), 1975. 296 pages, $14.50.

PRINCIPLES OF CLINICAL ELECTROCARDIOGRAPHY—Ninth Edition—Mervin J. Goldman, MD, Clinical Professor of Medicine, University of California, San Francisco. Lange Medical Publications, Drawer L, Los Altos, CA (94022), 1976. 412 pages, $9.50.

PROGRESS IN HEMOSTASIS AND THROMBOSIS—Volume 3—Edited by Theodore H. Spaet, MD, Head, Hematology Division, Montefiore Hospital and Medical Center, Professor of Medicine, Albert Einstein College of Medicine, Bronx. Grune & Stratton, Inc., Medical and Scientific Publishers, 111 Fifth Avenue, New York City (10003), 1976. 342 pages, $31.50.

REALITIES OF NUTRITION—Ronald M. Deutsch. Bull Publishing Co., P.O. Box 208, Palo Alto, CA (94302), 1976. 405 pages, $9.95.

RECENT ADVANCES IN ANAESTHESIA AND ANALGESIA—Number Twelve—Edited by C. Langton Hewer, MB, BS(Lond), MRCP(Lond), Hon FFARCS(Eng), Consulting Anaesthetist to St. Bartholomew's Hospital and to the Hospital for Tropical Diseases, London; and R. S. Atkinson, MA, MB, BChir, FFARCS, Consultant Anaesthetist, Southend General Hospital, Essex. Churchill Livingstone Medical Division, Longman, Inc., 19 West 44th St., New York City (10036), 1976. 268 pages, $29.50.

RECENT ADVANCES IN CLINICAL PSYCHIATRY—Number Two—Edited by Kenneth Granville-Grossman, MD(Lond), FRCP, FRCPsych, Consultant Psychiatrist, St. Mary's Hospital, London. Churchill Livingstone Medical Division, Longman, Inc., 19 West 44th St., New York City (10036), 1976. 358 pages, $38.00.

RECENT ADVANCES IN RHEUMATOLOGY—Part 1: Underlying Mechanisms of Disease—Part 2: Clinical Features and Treatment—Edited by W. Watson Buchanan, MD, FRCP, Professor of Medicine, Centre for Rheumatic Diseases and University Department of Medicine, Royal Infirmary, Glasgow; and W. Carson Dick, MD, MRCP, Honorary Clinical Lecturer, Department of Medicine, University of Glasgow, Consultant Physician, Centre for Rheumatic Diseases and University Department of Medicine, Royal Infirmary, Glasgow. Churchill Livingstone Medical Division, Longman, Inc., 19 West 44th St., New York City (10036), 1976. Part 1: 214 pages, $24.50; Part 2: 218 pages, $24.50.

RECENT ADVANCES IN UROLOGY—Number Two—Edited by W. F. Hendry, ChM, FRCS, Consultant Urologist, St. Bartholomew's Hospital, Royal Marsden Hospital and Chelsea Hospital for Women; Senior Lecturer, Institute of Urology, London. Churchill Livingstone Medical Division, Longman, Inc., 19 West 44th St., New York City (10036), 1976. 353 pages, $32.50.

REVIEW OF MEDICAL MICROBIOLOGY—Twelfth Edition—Ernest Jawetz, PhD, MD, Professor of Microbiology and Chairman, Department of Microbiology, Professor of Medicine, Lecturer in Pediatrics, University of California School of Medicine, San Francisco; Joseph L. Melnick, PhD, Distinguished Service Professor of Virology and Epidemiology, Baylor College of Medicine, Houston; Edward A. Adelberg, PhD., Professor of Human Genetics, Yale University School of Medicine, New Haven. Lange Medical Publications, Drawer L, Los Altos, CA (94022), 1976. 542 pages, $10.00.

SO GET ON WITH IT—A Celebration of Wheelchair Sports—Marilee Weisman & Jan Godfrey. Doubleday & Company, Inc., 245 Park Avenue, New York City (10017), 1976. 159 pages, $8.95.

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REVIEW OF MEDICAL PHARMACOLOGY—Fifth Edition—Frederick H. Meyers, MD, Professor of Pharmacology; Ernest Jawetz, PhD, MD, Professor and Chairman, Department of Microbiology, Professor of Medicine and Lecturer in Pediatrics; and Alan Goldfien, MD, Professor of Medicine, Departments of Medicine and Obstetrics & Gynecology and Cardiovascular Research Institute, University of California, San Francisco. Lange Medical Publications, Drawer L, Los Altos, CA (94022), 1976. 740 pages, $12.50.

SOLVED: THE RIDDLE OF HEART ATTACKS—Broda O. Barnes, MD, PhD, and Charlotte W. Barnes, AM. Robinson Press, Inc., Fort Collins, CO (80522), 1976. 84 pages, $2.50 (Paperback).

STANDARD ORTHOPAEDIC OPERATIONS—A Guide for the Junior Surgeon—John Crawford Adams, MD(Lond), MS(Lond), FRCS(Eng), Consultant Orthopaedic Surgeon, St. Mary's Hospital, London; Civil Consultant in Orthopaedic Surgery, Royal Air Force; Production Editor, **Journal of Bone and Joint Surgery.** Churchill Livingstone Medical Division, Longman, Inc., 19 West 44th St., New York City (10036), 1976. 384 pages, $29.50.

TETRAPLEGIA AND PARAPLEGIA—A Guide for Physiotherapists—Ida Bromley, MCSP, Superintendent Physiotherapist, Stoke Mandeville Hospital, Aylesbury; illustrated by Janet Plested, AIIP, AMPA; Foreword by Sir Ludwig Guttmann, CBE, MD, FRCP, FRCS. Churchill Livingstone Medical Division, Longman, Inc., 19 West 44th Street, New York City (10036), 1976. 242 pages, $13.50.

TEXTBOOK OF PAEDIATRIC NUTRITION—Edited by Donald S. McLaren, MD(Ed), PhD(Lond), DTM & H(Eng), Professor of Clinical Nutrition and Director of the Nutrition Research Program, the School of Medicine and American University Hospital, American University of Beirut; and David Burman, BSc, MD, FRCP, DCH, Consultant Paediatrician, Bristol Royal Hospital for Sick Children, St. Michael's Hill, Bristol, Clinical Lecturer in Child Health, University of Bristol. Churchill Livingstone Medical Division, 19 West 44th St., New York Cty (10036), 1976. 416 pages, $35.00.

TRAUMATIC NERVE LESIONS OF THE UPPER LIMB—Edited by J. Michon and E. Moberg. Monographs of the Group d'Etude de la Main Series edited by R. Tubiana. Churchill Livingstone Medical Division of Longman, Inc., 19 West 44th Street, New York City (10036), 1976. 110 pages, $29.50.

TROPICAL DISEASE—Fifth Edition—Frederick J. Wright, MD(Cantab), FRCP(Edin), FRCP(Lond), DTM, HEng, Head of Medical Department, Kilmanjaro Christian Medical Center, Moshi, Tanzania; and Sir James Baird, KBE, MD, FRCP(Edin), FRCP(Lond), Lieutenant-General, late RAMC Director-General of Army Medical Services; Formerly Professor of Military Medicine of the Royal Army Medical College and the Royal College of Physicians, London. Supplement to **DAVIDSON'S PRINCIPLE AND PRACTICE OF MEDICINE—Eleventh Edition**—Edited by John Macleod. Churchill Livingstone Medical Division, Longman, Inc., 19 West 44th St., New York City (10036), 1975. 147 pages, $8.50.

THE WILMER OPHTHALMOLOGICAL INSTITUTE—The First Fifty Years 1925-1975—M. Elliott Randolph, MD, Associate Professor Emeritus of Ophthalmology, the Johns Hopkins University; and Robert B. Welch, MD, Associate Professor of Ophthalmology, the Johns Hopkins University. The Williams & Wilkins Company, 428 E. Preston St., Baltimore (21202), 1976. 216 pages, $12.00.

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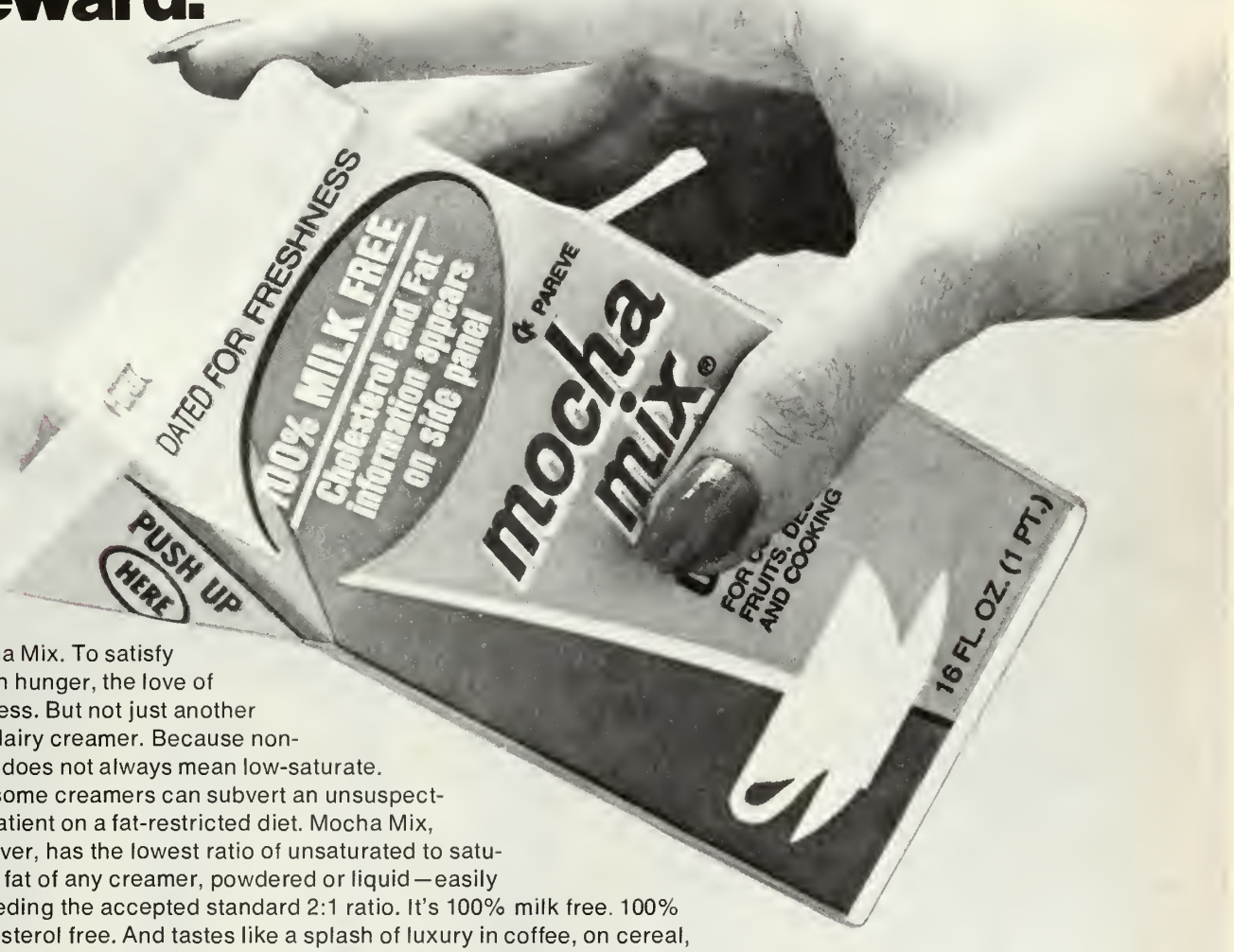

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Graded Treadmill Stress Testing

Patterns of Physician Use and Abuse

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Treadmill stress testing is used in assessing the condition of patients with known or suspected heart disease. We did a prospective study to clarify physician ordering and integration of the test. Ordering criteria were always complied with, although most tests were ordered for evaluation of atypical chest pain and only a few for high risk patients with known cardiac dysfunction, indicating a misplaced emphasis on the diagnostic capabilities of the test. Tests in patients with atypical chest pain and stress-induced ischemic changes were always integrated, but in 30 percent of patients with atypical pain and no stress-induced electrocardiographic changes, the tests were not used in patient management. This was often due to the misconception that negative findings on a stress test excluded coronary disease. Physicians should be alerted to this misplaced emphasis and misconception.

As EMPHASIZED in a host of publications, the major uses of graded treadmill exercise stress testing are assisting physicians in substantiating a diagnosis of myocardial ischemia, establishing an anginal threshold level, provoking exercise-induced arrhythmias, establishing a level of activity after recovery from myocardial infarction, providing an objective index of effectiveness of therapy and reassuring an anxious patient, among others.[1-5] However, few authors examine the actual utilization of treadmill tests. The prospective study reported here evaluated the pattern of physician use of graded treadmill exercise stress tests.

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Materials and Methods

The study had two purposes: (1) to determine if the relatively expensive graded exercise tests are ordered for appropriate reasons at San Francisco General Hospital and (2) to find if the information obtained from the tests affect, in any way, patients' subsequent management. Therefore, we designed the study using a prospective format in which acceptable criteria for ordering the test and acting upon the results were determined before initiation of the test.[6,7] In order to make the experiment both relevant and educational, the predetermined criteria were established by both house staff and attending physicians before the inception of the study; they are outlined in Tables 1 and 2. We attempted to further ensure general acceptance of the ordering and action criteria via a staff conference on graded treadmill testing, which ensured wide promulgation to the

house staff and attending physicians. Because most of the tests were ordered by the physicians in the outpatient division, collection of data was facilitated because outpatient care for each patient is the continuous responsibility of one house officer under staff supervision, and the problem-oriented medical record is used throughout the hospital.

All graded exercise tests done in the cardiopulmonary unit at San Francisco General Hospital between July 1, 1974 and June 30, 1975 were examined. At this teaching medical facility, all exercise tests are ordered by interns, residents and staff physicians. A physician telephones the cardiology secretary and asks her to schedule an exercise appointment. Subsequently, he must also complete an official request and mail it to the staff cardiologist who carries out the test. This request form includes a succinct outline of the type of patient who is a subject for testing. The form strongly implies that the test should be used in patients with known cardiac disease. It is not required that any test request be approved by the cardiology staff physician.

Each patient referred for testing was interviewed, examined and stress tested by one of the authors (J.A.). Before each test, the reason for the test was ascertained, the patient signed an informed consent and a resting 12-lead electrocardiogram was done immediately before testing. Testing was done on a Quinton treadmill, model No. 18-54. The exercise stages were adapted from the recommendations of Sheffield,[8] and consisted of three minutes of exercise, at each sequential stage, starting first at 1.5 miles per hour (mph) and a 10 percent grade, then at staged increments of 1 mph to a maximum of 4.5 mph or the rate of speed that is just below that when the patient must jog. Thereafter, exercise stages were achieved by increasing the incline of the treadmill from a 10 percent grade at Stages I through IV to more steep grades at increments of 2.5 percent per exercise level. Electrocardiographic monitoring was accomplished by a single bipolar precordial lead system of the type recommended by Ellestad and co-workers[9] and by a tachometer, oscilloscope, and continuous strip chart and magnetic tape recordings.[9] Blood pressure was recorded by sphygmomanometer before, at each exercise stage during and immediately after exercise, and every two minutes thereafter for 11 minutes. Exercise was continued until the patient achieved 90 percent of the maximum predicted heart rate or developed untoward symptoms, including an anginal syndrome, frequent ventricular irritability, arterial hypotension, extreme fatigue, breathlessness, or lightheadedness. Patient safety was emphasized.

The patterns of the electrocardiographic ST segments—including those at rest, at the third minute of each exercise stage, at the peak exercise achieved, and at each minute after exercise for 10 minutes—were reviewed independently by two of the authors (J.A. and M.C.).* Using the criteria of Ellestad, the exercise test was considered positive for ischemia when ST-segment depression of

*The two cardiologists reviewing the stress tests for positivity or negativity of ST-segment depression in the atypical angina subgroup of patients agreed in 41 instances (78 percent) and disagreed in 11 (21 percent). These findings are much better than those reported by Blackburn and co-workers[10] for non-computerized methods of stress testing interpretation and internally invalidated the testing procedure.

TABLE 1.—*Acceptable Criteria for Ordering Graded Treadmill Tests*

Attempting confirmation of diagnosis of angina that is uncertain from the clinical history.
Evaluating whether arrhythmias improve or worsen with effort.
Ascertaining appropriate postmyocardial infarction exercise prescription.
Screening high risk patients—namely those with stable angina pectoris who are at high risk of having severe three-vessel coronary disease or its equivalent and symptomatic patients at high risk of having coronary disease, such as firemen, policemen, persons with diabetes or hypertension, and persons with strong family history of coronary disease.
Evaluating the results of antianginal therapy, including drugs and surgical procedures.
Evaluating for industrial or disability purposes.
Evaluating selected patients with aortic stenosis, subaortic stenosis or mitral valve disease.
Reassuring anxious patients without heart disease.

TABLE 2.—*Acceptable Criteria for Integrating Graded Treadmill Test Results*

If test result is positive:
- Medical or surgical therapy is initiated or continued.
- Physician restricts or liberalizes patient activities.
- Coronary angiography is advised and carried out.
- Medical strategy is changed.

If test result is negative, borderline or inconclusive:
- The clinical diagnosis of heart disease is still certain and the physician proceeds as in above.
- The clinical diagnosis of heart disease is excluded and the physician seeks another cause for the patient's complaints and discontinues therapy for heart disease.
- The clinical diagnosis of heart disease is unresolved and the physician orders further diagnostic tests which may include coronary angiography. Further drug therapy for arteriosclerotic heart disease is legitimate only if the reason is explicitly stated in medical records and the patient responds to this drug therapy.

at least 0.1 mV in depth lasting for at least 0.08 seconds was present on any of the exercise or recovery tracings.[11] Arrthythmias were tabulated, where appropriate, and observations regarding development of congestive heart failure and state of physical condition were made and reported. When the cardiologists disagreed with the interpretation of electrocardiographic changes, the opinion of the testing cardiologist was used in the final report. All exercise test reports were telephoned to the ordering physician without any judgmental statement regarding the necessity for the test or suggestions for future patient management, and a typed report was placed in the patient's medical record to ensure that the results reached the attending physician. This report emphasized the duration of exercise for symptoms or ischemia to develop (a reflection of the patient's cardiac disability) or if the patient achieved 90 percent of maximum heart rate, the duration of exercise was related to physical fitness. If other adverse or untoward effects developed, such as an inordinant rise or fall in blood pressure, excessive fatigue or exhaustion, cerebral symptoms or heart failure, then these aspects of the test were also duly reported in the typed report.

After a minimum of one month, the charts of all subjects were analyzed by two of the authors (J.A. and M.T.) for acceptable integration of the test results into patient management using the predetermined appropriate action criteria. The action criteria were liberally interpreted so that a physician's response was deemed appropriate if it could be inferred from the actual course that transpired or from the physician's ordering of medications even if it was not explicitly stated in the medical record. These included continuing or discontinuing therapy, carrying out coronary angiography and limiting or liberalizing exercise (Table 2).

Results

In all, 90 graded treadmill tests were done during the study period and reviewed; 86 of the patients were referred from the outpatient division. Of the tests, 40 were ordered by members of the house staff; the remainder by cardiac or medical full-time staff physicians. The reasons for ordering the tests are summarized in Table 3. Most of the tests were ordered to assist in resolving the problem of chest pain (60 percent), but relatively few were ordered for evaluating high risk patients (18 percent) including patients with known angina pectoris, diseases that predispose to coronary artery disease such as hypertension and diabetes, postmyocardial infarction and arrhythmias. However, at least one of the predetermined acceptable criteria for ordering the treadmill exercise tests was met in each instance; no test was ordered that was inappropriate. Because the group of patients with chest pain of uncertain cause, possibly atypical angina, was the largest studied, each of these patients' medical records was reviewed for integration of the test results into patient management. In this review the predetermined acceptable criteria of physician action were used. Only 52 charts for the 54 patients in this subgroup were available for review. The numbers of patients in each of the remaining seven categories were too few to yield significant data.

TABLE 3.—*All Graded Exercise Treadmill Tests Done at San Francisco General Hospital From July 1, 1974 to June 30, 1975*

Physicians' Reasons for Ordering Test	*No. of Patients*	*Percent*
Chest pain—atypical angina pectoris	54	60
Arrhythmias improve or worsen	11	12
Postmyocardial infarction	5	5
Classic angina pectoris	1	1
Evaluate medicine and/or surgical coronary therapy	5	6
Functional evaluation	6	7
Valvular and congenital heart disease	5	6
Reassurance of anxious patient	3	3
TOTAL	90	100
Acceptable reasons for ordering test	90	100

Although all 52 patients were referred for evaluation of chest pain atypical of angina pectoris, the interview before the test often showed a syndrome completely compatible with angina—that is, exercise or mental stress resulted in a precordial sensation of chest heaviness or tightness that was self-limited, lasted less than 20 minutes or was relieved with the sublingual use of nitroglycerin. Twelve such patients were identified; the variability of the physician-patient interview in obtaining historical documentation of the anginal syndrome has been discussed by others.[12] Atypical angina was presumed present if some of the patient's complaints were compatible with, but unusual for, the anginal syndrome, such as sharp rather than heavy or constricting precordial pains, symptoms present at rest but not exercise, or pain limited to a localized area over the apex of the heart. Because no significant differences were noted when the results of physician integration of the test into patient management were tabu-

lated for those patients who had clear-cut angina or for those who had atypical angina, the results were grouped for the sake of clarity.

The results showed that when the graded treadmill test was positive for ischemic ST-segment depression in six of 52 instances, acceptable criteria for integration of the test results into patient management were always met. However, when the ST-segment depression was negative (39 of 52) or borderline (seven of 52), an inordinate number of physicians did not integrate the exercise data into patient management (Table 4).

A total of 39 graded treadmill stress tests were negative for ischemic ST-segment depression or development of a typical anginal syndrome in patients referred for atypical chest pains. In 26 (67 percent), physician integration of the results was appropriate. The reason for the appropriate physician action did not have to be stated explicitly in the hospital record but at a minimum could be inferred by the reviewers from subsequent physician actions, whether diagnostic or therapeutic, including prescribing behavior.

In 13 instances (33 percent), inappropriate physician action was judged present. In 11, the test results were not integrated into patient management in any explicit or implicit fashion even though the symptoms of chest pain prompted the patients to seek medical attention and persisted in all; neither cause of the complaints was determined nor was symptomatic therapy to relieve them instituted. Subsequent personal interviews with the attending physicians caring for these patients showed that the physicians believed a negative graded exercise test excluded any possibility of coronary artery disease and that consequently their patients' chest complaints could not be due to cardiac disease; no further attempt was made to find out the origin of the patients' symptoms. In two patients, the test results explicitly mentioned the exclusion of coronary artery disease, but in spite of this, antianginal therapy was continued. The rationale for doing this and the results of such treatment were unclear. The staff caring for these 13 patients included ten interns, one resident, one cardiac fellow and one medical attending staff physician.

In six subjects, the graded treadmill exercise tests were positive for ischemic ST-segment depression, and in each subject appropriate physician action (as determined by the ordering physicians before the initiation of the study) followed the reporting of the patient's exercise test (Table 2). In three patients with ischemic response, typical angina developed at the time of stress testing. In one the test resulted in restriction of activities, in the second propranolol was added to nitroglycerine therapy and in the third the magnitude of the ST depression played a role in the decision to carry out coronary cineangiograms during which significant three-vessel disease was found.

TABLE 4.—*Integration of Exercise Test Results into Management of 54 Patients with Atypical Angina at San Francisco General Hospital From July 1, 1974 to June 30, 1975*

		Appropriate Integration		*Inadequate Integration*	
Test Results	*No. of Patients*	*No. of Patients*	*Percent*	*No. of Patients*	*Percent*
Positive	6	6	100	0	0
Negative	39	26	67	13	33
Borderline or Inconclusive	7	5	72	2	28
TOTAL	52	37		15	
Charts not located	2				

Three of the six patients with ischemic responses reproduced their atypical anginal symptoms with effort. In one with 1-mm exercise-induced, ST-segment depression, coronary cineangiography was done because of persistence of chest pain unresponsive to medical management and a low grade stenosis of the right coronary artery proximal to the crux was shown. In the second patient, a mitral valve prolapse syndrome was diagnosed clinically and verified by echocardiography. Although it was never determined whether or not the positive ischemic response to exercise was falsely positive in the third, medical therapy with nitroglycerin successfully relieved the symptoms.

Discussion

These results show that the physicians ordering the graded treadmill exercise test were totally in compliance with explicit and predetermined ordering criteria. This is in harmony with findings of other medical care audits regarding ordering patterns from this hospital.[7] In addition, compliance was in no way affected by preselection, because the cardiology division did not screen for approval the tests scheduled by the ordering physicians. When medical use of one specific laboratory test (versus panels of laboratory tests) is audited, malutilization of the test is more a subtle phenomenon than heretofore emphasized.

We have previously noted that malutilization of specific laboratory tests is often due to lack of integration of the test results into patient management.[7] Regarding graded treadmill exercise testing, failure to exercise high risk and known coronary patients and failure to always properly integrate the results into patient management appeared to be caused by a dual misconception on the part of the patients' physicians.

The first misconception, which was derived from physician interview of the 11 patients in whom there were negative stress test results but in whom symptoms persisted, is the idea that exercise stress testing is the definitive noninvasive tool to verify the existence, or exclude the presence, of ischemic coronary artery disease. Although we concur that stress testing should be used to evaluate atypical chest pain, our results show that at our hospital inordinate emphasis is placed on treadmill tests to resolve these questions concerning coronary disease.

In six patients the exercise test gave positive findings, indicating to the referring physician that coronary disease was responsible for the patient's complaints. Although the number of patients was small, 100 percent compliance with the explicit predetermined integration criteria was always present and management goals were clear to the physician. In those patients with possible but atypical angina, a negative finding on a graded treadmill test too often resulted in less clearly defined diagnostic and subsequent therapeutic maneuvers. In 30 percent, this led to physician reassurance that the patient's symptoms were not due to a cardiac cause; even though the complaints persisted, the exercise test was the only diagnostic test ordered. No further therapy, even symptomatic treatment, was prescribed. In these patients, the physicians concluded that a negative finding on a treadmill test definitely excluded the presence of coronary artery disease. Patently, this attitude is fallacious, because it has been amply shown that ST-segment depression during exercise testing correlates to a high degree with the presence of significant and severe coronary artery disease in two or three vessels, but the absence of such depression does not exclude it.[13] Borer and co-workers[14] recently reemphasized this point when they found negative exercise tests in 39 percent of patients with angiographically documented severe coronary disease and typical angina. When there is less clear-cut historical information suggesting angina, there is also a lower probability that stress testing will resolve the issue of the presence or absence of coronary disease.[15] Because there is ample evidence that coronary angiography has a significant morbidity and mortality as well as expense, the physician's attitude toward subjecting all patients with possible atypical angina to coronary angiography is natural. Possibly, stress testing combined with radioisotope scanning of the heart will increase the sensitivity of noninvasive diagnosis in such patients.

The second misconception we encountered in our hospital is that there is little practical benefit from exercise testing subjects with known coronary artery disease, especially those with stable angina pectoris or recovered myocardial infarction. It must be emphasized that this is not a result of our failure to see large numbers of patients with coronary artery disease because 200 patients with acute myocardial infarction were admitted, treated and discharged from the hospital during the study period, nor is it a result of our explicit teaching. We believe it reflects our failure to communicate the proper emphasis of the ordering criteria. Only one patient with healed myocardial infarction was referred for exercise testing during the study year.

There is ample evidence that the patients most in need of graded treadmill stress testing are those with known coronary artery disease. For example, we believe that any patient, even one with stable angina, in whom pronounced ST-segment depression is noted during graded treadmill testing may be a serious candidate for coronary angiography if only because pronounced ST-segment depression has been shown to correlate well with left main stem or three vessel coronary disease, lesions which may be surgically remediable.[16] In addition, we believe that exercise testing is clearly called for in a patient who has recovered from an acute myocardial infarction in order to assist the attending physician in prescribing a rational and safe rehabilitation program.

Although we concur that graded treadmill stress tests certainly should be used to evaluate patients with atypical chest pain, we conclude that stress testing is used inordinately as the definitive test in the differential diagnostic workup of these patients. On the other hand, stress testing is underused in those patients with known and stable coronary disease especially those with angina or healed myocardial infarction. Too often a negative stress test result is ignored and used only by the ordering physician to reassure himself that

a patient does not have severe coronary disease and it is not used in guiding management of the persistent symptoms after the test is completed.

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A Reliable Method of Determining Intravascular Volume

We find the most reliable method for following a patient's intravascular volume is the measurement of the blood pressure in two positions, mainly looking for postural hypotension. If I had to have one clinical method, I would take that. You can't use the dryness of the mouth to determine dehydration because some patients are mouth-breathers and they all have dry mouths, or many of them do. You can't use axillary perspiration . . . But the most reliable thing clinically is to measure their blood pressure lying in bed and sitting up with their feet dangling. Now, it isn't enough just to have them sit up in bed. They must dangle their feet. I must agree that occasionally you may have a problem with an old person who has been lying in bed for many months and suddenly you rush in and have the patient sit up. That may be the last time you examine him. Obviously, you must pick your case. But if you get greater than a 20 mm drop of mercury mean pressure, you would then have a pretty good indication that the patient has hypovolemia. Now, there are certain problems here . . . Again if the patient is an old person and has been lying in bed for a very long time, you may get a postural drop and he may not be hypovolemic. If the patient has autonomic dysfunction (diabetes, let's say), you may get a postural drop and he may not be hypovolemic. The clue here is, of course, that the pulse rate will not go up. You may also be fooled by a patient who is taking an antihypertensive drug, such as methyldopa (Aldomet®), which produces postural hypotension. But again, the best clinical guide we have is this postural change.

—NORMAN LASKER, MD, *Philadelphia*

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Myocardial Revascularization in Patients 70 Years of Age and Older

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Myocardial revascularization has been carried out by us in 67 patients 70 years of age or older. Advanced coronary artery disease was found at angiography in more than two thirds of the patients. The postoperative morbidity and mortality compare very favorably with those in younger patients. The early and late mortality in the 67 patients was 4.5 percent and 6.0 percent, respectively. Fifty-seven survivors have been followed an average of 21 months; for most patients there has been a pronounced improvement in clinical classification. Properly selected, patients of advanced age can undergo successful revascularization surgical procedures. The adequacy of function of the left ventricle, proper timing of the surgical operation and an aggressive yet realistic approach seem to be major determinants for a good result.

MYOCARDIAL REVASCULARIZATION using the reversed autogenous saphenous vein technique has become an established form of treatment for symptomatic ischemic coronary artery disease. As experience increases, the indications for this surgical procedure are becoming more refined while, at the same time, the operation is being extended to others, particularly older patients. This is due in part to the increasing safety of the procedure as surgical teams become more experienced in the techniques of revascularization, including myocardial protection during the bypass procedure, as well as the excellent preoperative and postoperative care given these patients in coronary care and cardiac surgical units.

Of particular interest to us has been revascularization operations in older patients. In 1973 we reported experience with 100 patients aged 65 years and older in whom surgical operation was carried out for coronary artery disease and its complications.[1] Others also have reported that cardiac surgical procedures, including revascularization, can be done in older patients with acceptable morbidity and mortality, and excellent long-term results. The basis for this report is an analysis of 67 patients 70 years of age or older, who underwent myocardial revascularization for coronary artery disease. These patients represent a very select group, inasmuch as no patient is included who had myocardial resection or valve replacement for complications of coronary artery disease. This group affords a valid comparison to patients of a younger age, since the most widely performed operation for coronary artery disease is myocardial revascularization alone.

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Clinical Data

From June 1969 to October 1975 myocardial revascularization alone was carried out in 1,886 patients for coronary artery occlusive disease. Of these, 67 (3.6 percent) were 70 years of age or older. The ages ranged from 70 to 81, with an average of 72.4 years. There were 51 men and 16 women. In more than two thirds (67 percent) of the patients angina occurred at rest or was of recent onset, factors believed to be associated with severe coronary artery disease. In 21 patients there was a history of antecedent myocardial infarction. In eight patients there was a history of heart failure, a bad prognostic sign in coronary artery disease. In four patients there were severe, life-threatening arrhythmias, and in two these were the only indication for surgical operation (Table 1). Two patients were referred for operation after a diagnosis of ischemic coronary artery disease was made during evaluation for surgical treatment of abdominal aneurysm. In one severe claudication of the lower extremities was present. No patient in this group had a history of hypertension or diabetes. Two were considered in Class II, 48 in Class III, and 17 in Class IV (New York Heart Association classification).

In all coronary cineangiography and ventriculography were done before operation. The cineangiography showed the presence of advanced coronary artery disease in 77 percent of the patients. In these patients either triple vessel disease or significant left main coronary artery obstruction, often of a very high degree, was present together with right coronary artery obstruction. In the remainder there was either proximal left anterior descending lesions or two vessel disease. Ventricular performance was interpreted as normal in 30 patients. Segmental dysfunction was present in 29 patients and in 8 the ventricle was generally hypocontractile (Table 2).

TABLE 1.—*Cardiac Findings in 67 Patients*

Angina	
At rest	45
With exercise	10
Of recent onset	6
Previous myocardial infarction	21
Heart failure	8
Arrhythmia, severe	4

TABLE 2.—*Angiographic Findings in 67 Patients*

Extent of Disease	*Number of Patients*	*Ventricular Function*		
		Normal	*Fair*	*Poor*
Single vessel (LAD)	7	6	1	..
Two vessel	8	6	2	..
Three vessel*	52	18	26	8

*Includes 22 with left main coronary artery disease.

TABLE 3.—*Postoperative Complications in 23 Patients*

Arrhythmia	13
Postoperative bleeding requiring reoperation	4
Respiratory insufficiency	4
Congestive heart failure	2
Myocardial infarction	1
Renal failure	1
Thrombophlebitis	1
Pulmonary embolism	1
Wound infection	1

Method

There were no emergency operations. Patients with unstable anginal symptoms or life-threatening lesions (especially left main coronary artery obstructions), or both, were operated on an urgent basis.

Our surgical technique has been modified since our 1973 report, essentially to provide better myocardial protection during the revascularization. All operations are carried out using cardiopulmonary bypass with a disposable bubble oxygenator and hemodilution. The ascending aorta is cannulated routinely and a single right atrial cannula is used. The left ventricle is always vented through the right superior pulmonary vein. Moderate core cooling to 28°C is achieved. In addition, local cooling of the heart with topically administered saline at 4°C is used to protect the myocardium during the periods of ischemic cardioplegia. The distal anastomoses are done with a quiet heart by intermittent cross clamping of the aorta; the individual cross-clamp times are of approximately 15 minutes' duration. The aortic anastomoses usually are done after the completion of each distal anastomosis, employing partial side-biting of the aorta to permit resumption of myocardial blood flow and thus repay the myocardial oxygen debt. While separate grafts are used most commonly, sequential grafts are done with increasing frequency in an attempt to revascularize more vessels and to enhance the flow in the grafts by providing more runoff. This is in keeping with the concept of total revascularization. All anastomoses are carried out using interrupted suture of 6-0 and 7-0 synthetic material.

TABLE 4.—*Cause of Death in Seven Patients*

Early		
Left ventricular failure	3	
Intraoperative	1	
Early postoperative	2	
		3 (4.5%)
Late		
Heart failure	1	
Sudden death	1	
CVA	1	
Unknown	1	
		4 (6.0%)

The average cardiopulmonary bypass time rarely exceeds 90 minutes for complete revascularization. A total of 154 saphenous vein bypass grafts were done in the 67 patients, an average of 2.3 grafts per patient. Four internal mammary-coronary artery anastomoses were carried out.

Results

Postoperative nonfatal complications occurred in 23 patients (Table 3). The most frequent complication was minor arrhythmia. In four patients reexploration was required for excessive bleeding early in the postoperative course. Respiratory insufficiency requiring ventilatory support for a period not exceeding 48 hours was present in four patients; no tracheostomies were required.

Three patients died in the early postoperative period, a mortality of 4.5 percent (Table 4). All these deaths were due to left ventricular failure. Early in our experience, a patient with left main coronary artery disease and a normal ventricle could not be taken off bypass after having three grafts. Normothermic perfusion was used and no form of myocardial protection offered. Two patients with severe diffuse three-vessel disease, generally hypocontractile ventricles and a history of failure constitute the other early postoperative deaths. In one of these patients extensive right coronary artery endarterectomy was required because of diffuse disease in addition to saphenous vein bypass grafting. The patient died from left ventricular failure on the first postoperative day. An extensive recent thrombus, extending up to the distal point of the endarterectomy, and a recent infarct were noted. The other early death was also due to left ventricular failure.

There have been four late deaths; two patients died as a consequence of their disease, assuming that the patient in whom sudden death occurred died of an arrhythmia (Table 4). Both these patients had triple vessel disease; one patient received three grafts, the other four. One other patient succumbed to a cerebrovascular accident, and the cause of death in the fourth patient remains unknown. These four late deaths represent a late mortality of 6 percent, and a cumulative mortality of 10 percent for the entire group.

Continued yearly follow-up of 57 of the survivors is being carried out. They have been followed for a period varying from three months to 54 months, with an average of 21 months. The data on three others remain inconclusive and hence are not included. There have been three late myocardial infarctions in three patients; in another patient a subdural hematoma developed in an auto collision while on a regimen of anticoagulants. All four patients survived. In one patient with an abdominal aneurysm an operation has been successful, while the other person with a similar aneurysm awaits operation. Aortoiliac reconstruction has been carried out in a woman with severe lower extremity claudication and the patient has made an uneventful recovery. All patients improved with the exception of two in Class II and two in Class III (Figure 1). The two patients in Class II were operated upon in anticipation of later operation for abdominal aneurysms. Their cardiac symptoms remain unchanged. In two patients in Class III there was preoperative impairment of left ventricular function; both continue to be moderately incapacitated. Most of the patients were very grateful and thought the operation worthwhile, permitting as it did most of them to resume normal activity.

Eight patients have been restudied, and 15 of

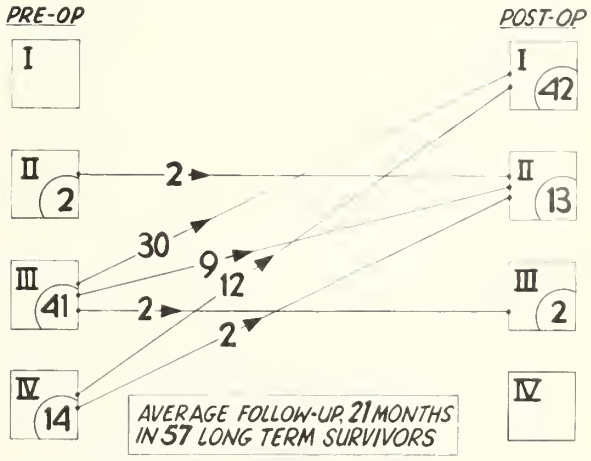

Figure 1.—Clinical classification (New York Heart Association) of 57 long-term survivors. See text for explanation.

16 bypass grafts are patent. Restudy was done because of recurrent angina in two patients, and as part of a routine late postoperative evaluation in the others.

Discussion

Cardiac surgical procedures in the elderly, though associated with an increased risk, can be carried out with an acceptable morbidity and mortality.[1-4]

Our experience, reported here, with patients 70 years of age and older who have symptomatic coronary artery disease shows that these patients can be expected to do as well as younger patients, provided rigid indications for operation are maintained. The 27 complications occurring in the 23 patients makes a complication rate of 33 percent. In our group of patients less than 70 years of age, the complication rate is 27 percent, somewhat lower. The nature of the complications is the same in both groups. Of note, however, is an incidence of 1.5 percent cerebrovascular accident and 0.82 percent of sternal dehiscence in the younger group. Neither of these problems occurred in the patients older than 70. Postoperative ionotropic support in this small group was unusual. Most of these patients have been operated upon since 1973, when we began using core cooling and topical cooling of the heart. This form of myocardial protection enhances, we believe, postoperative left ventricular function and decreases the need for such ionotropic support.[5] The incidence of early postoperative myocardial infarction is 1.4 percent in both groups.

The early postoperative deaths in this series were attributable to factors that could have been altered. The one patient with left main coronary artery disease and a normal ventricle was operated upon early in our experience. No type of myocardial protection was carried out and the deterioration in ventricular function, which prevented removing the patient from cardiopulmonary bypass, was probably avoidable. The two patients with severe left ventricular dysfunction probably should not have been operated upon. These two deaths cannot be ascribed to advanced age, since three vessel coronary artery disease with a generally hypocontractile ventricle causes a similarly high surgical risk regardless of a patient's age.[6] Comparison of the early and late mortality in the 67 patients with those of the patients under 70 years (1,819 patients) is given in Table 5.

TABLE 5.—*Comparison of Early and Late Mortality*

	Patients Under 70	*Patients 70 and Over*
Number of patients	1,819	67
Early deaths	3.1%	4.5%
Late deaths	4.6%	6.0%
Mortality rate	7.6%	10.0%

The very large proportion of severely symptomatic patients in this group, together with the findings of severe three vessel disease and a large number of left main coronary artery lesions, shows that in these elderly people surgical operation is needed to protect against a possible catastrophe. The lethal potential of significant left main coronary artery obstructions is well recognized.[7] For less symptomatic elderly patients, and there were few in this series, the quality of life desired by each patient should be a consideration when advising about surgical operation. To deny surgical treatment to a patient because of advanced age alone does not seem warranted based on these results. Medical treatment only should be reserved for elderly patients who have other system disease that militates against a major operation and for patients whose symptoms are such that they can be easily controlled.

From the standpoint of technique, there is no doubt that the proficiency of the surgical team shortens the operating time and decreases the period of myocardial ischemia while permitting maximal revascularization in the shortest operative time. Protection afforded the myocardium by core cooling and local cooling of the heart seems to decrease the injury incident to ischemic arrest. The proficiency of the anesthesiologists and of coronary care and cardiac surgical units helps in the common goal to minimize complications and improve survival.

The adequacy of revascularization by adhering to the concept of total revascularization is important.[8] Our experience with long-term follow-up of 929 patients in whom revascularization was done for triple vessel coronary artery disease shows that when complete revascularization is carried out the yearly death rate is 2.3 percent. This increases to 3.5 percent if only two vessels are revascularized and 7.7 percent if only one graft is placed.[9] The small number of patients in this study does not make a comparison possible, but it seems that this concept applies to all ages. In this group of patients the average number of grafts per patient was 2.3. In our first 1,650

myocardial revascularizations, the average number of grafts per patient also was 2.3. This implies that in older patients properly selected for revascularization there are an equal number of vessels suitable for bypass grafting as in younger patients.

There is no ideal age for myocardial revascularization. One must rely largely on the symptomatology, realizing that some characteristics of ischemic coronary artery disease, such as unstable angina or angina at rest, frequently are associated with severe coronary artery disease. In other cases, however, the degree of coronary occlusive disease found at the time of angiography will belie the clinical features. Certainly, in anticipation of a good result, all patients including older ones should be operated upon before myocardial damage becomes irreversible.

We believe another factor that has an adverse effect on the outcome is the urgency of the operation. We feel that early elective surgical operation should be done in patients with triple vessel disease or left main stem occlusion because of the increased risk of sudden death or myocardial infarction compared with that in patients with lesser extent of disease. The reluctance on the part of physicians and surgeons to consider surgical intervention in the elderly may jeopardize an otherwise excellent chance to obtain a good result. Urgent cases can become catastrophic emergencies if a rule of procrastination is allowed to prevail. This report deals with a select group of elderly patients. Proper case selection seems the main requisite to assure a good result keeping in mind, as in all age groups, that the main determinant of risk in coronary revascularization is the adequacy of the function of the left ventricle. By adopting a realistic, yet aggressive approach, patients of advanced age requiring myocardial revascularization can expect a result that is comparable with that in younger patients.

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Airway Management in Croup and Epiglottitis

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Treatment techniques for airway obstruction in croup and epiglottitis are reviewed in the medical literature. Series totaling 295 nasotracheal intubations, and 591 tracheostomies were reviewed. There were two deaths attributable to airway complications in 126 patients in whom nasotracheal intubation was carried out. In three patients subglottic granulation tissue and subglottic stenoses developed from short-term nasotracheal intubation. There were no subglottic stenoses or tracheal stenoses reported in the 591 tracheostomies. From this review, it would seem feasible to use nasotracheal intubation for short-term airway treatment in croup and epiglottitis. The increasing occurrence of laryngeal and tracheal complications with long-term intubation suggests that tracheostomy be considered in such cases.

TREATMENT OF croup and epiglottitis has undergone a long and significant metamorphosis. Morgan and Wishart cited a 75 percent mortality for these diseases in 1928. This rate was improved to nine percent in 1944.[1] At about the same time cure was achieved in 15 cases without the use of antibiotics, indicating that better airway care was responsible for the increased survival.[2]

Several series showed that tracheostomy was a quick and effective method for treatment of airway obstruction in children with these diseases. Holinger showed in 1950 that the infant glottis is comprised of an isosceles triangle with a length of 7 mm, a width of 5 mm and an area of 14 sq. mm (see Figure 1). If 1 mm of edema is projected on these measurements, the length becomes 5 mm and the area of the glottic chink only 5 sq. mm, a reduction of 65 percent.[3] The severity of obstruction induced by laryngeal edema in young children is evident.

Geraci has been credited with the first case report of nasotracheal intubation for croup and epigolottitis.[4] Actually, Striker first reported treatment of 11 such patients in 1967 in a series of 116 nasotracheal intubations.[5] Fearon reported follow-up and complications in 72 patients undergoing nasotracheal intubation for diseases other than croup and epiglottitis. He acknowledged the feasibility of this technique in treating patients with croup and epiglottitis, but included no such patients in his series.[6] Allen reported 61 patients undergoing nasotracheal intubation. He

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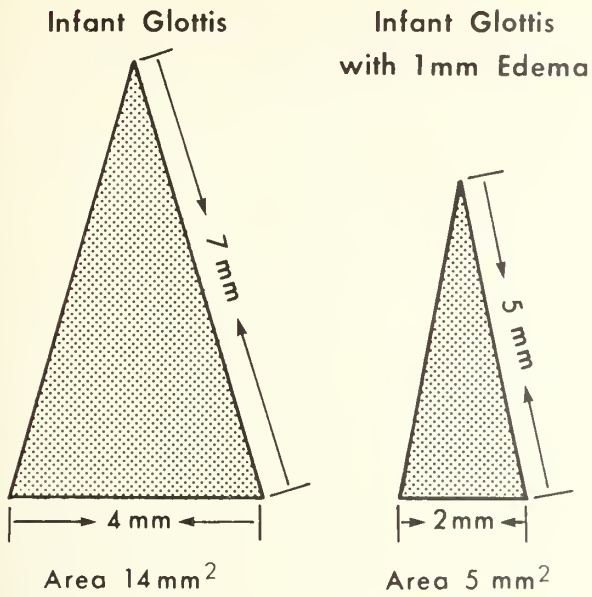

Figure 1.—Diagram of infant larynx, showing effect of edema on cross sectional area. (Adapted by permission from Holinger P: Factors responsible for laryngeal obstruction in infants. JAMA 143:1229, Aug 1950. Copyright 1950, American Medical Association)

found that in 23 of these patients reintubation was required and there was one death in his series.[7] In 33 of these patients elective follow-up laryngoscopies were done. Of these patients, 30 were normal at three months, and the conditions of the other three patients had returned to normal after six months. Tos reported the cases of 20 patients treated with nasotracheal intubation and noted nine airway complications.[8] These, however, were labeled "stridor only." He reported an average intubation time of 39 hours, and an average stay in hospital of 9.5 days.[9]

Battaglia treated 34 patients with nasotracheal intubation, finding the average intubation time was 2.8 days and the average time in hospital was 5.8 days. There was one death from airway obstruction in his series, but this occurred in a child being transported without a nasotracheal tube. He described two patients in whom subglottic granulation tissue developed, but did not note whether this progressed to subglottic stenosis.

Proponents of tracheostomy have also reported large series. In reviewing series of patients having tracheostomy for croup and epiglottitis, deaths occurring during "emergent" tracheostomy have been excluded. It has long been known that the treatment of epiglottitis by observation and tracheostomy on an *emergent* basis is associated with a pronounced increase in mortality. This is not the issue of this review. Baxter reported 100 tracheostomies without airway complications.[10] Rapkin (5 cases), Bass (16 cases), Freeland (14 cases), Margolis (15 cases) and Milko (32 cases) all reported tracheostomies without death from airway obstruction or other significant airway complications.[11-15] Freeland's series was complete with a long follow-up citing normal airway sizes after growth had occurred. Palva reviewed the cases of 47 patients in whom tracheostomy was carried out and reported four airway complications which were not completely described.[16] There was one death in his series attributable to tracheostomy when a cannula became obstructed in a patient being treated for subglottic stenosis. There was also one death resulting from "observation and emergency tracheostomy." Parton reported on 26 patients having tracheostomies.[17] There were two deaths in this series, both from emergency tracheostomy. Fearon's large series of 336 patients with croup and epiglottitis treated by tracheostomy had two deaths from airway obstruction.[18] Both of these deaths resulted from accidental extubation of the tracheostomy tube, a well-known complication of tracheostomy.

Proponents of nasotracheal intubation cite the following points in support of this treatment:

- No incision,
- No bleeding or pneumothorax,
- Decreased intubation and hospital time,
- Accidental extubation is not an emergency because the tube acts as an obturator of the airway.

Arguments against nasotracheal tube treatment include:

- Development of subglottic stenosis,
- Endolaryngeal injury,
- Nasal discomfort,
- Requires the same care as tracheostomy,
- The tube is in contact against the inflamed area of the primary disease.

In support of tracheostomy are the following arguments:

- It is a time honored and proven method with a low complication rate,
- There is no tube situated in the larynx or the area of inflammation,
- The diseased area is at rest,
- There is no nasal discomfort.

TABLE 1.—*Tabulation of all series reviewed. Column three (average tube time) is for intubation or tracheostomy. Note that seven deaths occurred in the tracheotomy series, while four occurred in intubated patients.*

Author	*Number of Cases Intubated*	*Number of Tracheostomies*	*Average Tube Time*	*Average Hospital Time*	*Accidental Extubation*	*Deaths*	*Airway Complications*	*Remarks*
Battaglia	34	.....	2.8 days	5.8 days	5	1	2	Airway complications due to subglottic granulation tissue. Death occurred enroute from one hospital to another.
Baxter	..	100	.....	.....	..	1	..	Death occurred during tracheostomy (emergent).
Coller	4	.....	3 days	.....	..	..	..	.....
Tos	20	.....	39 hours	9.5 days	1	..	9	Airway complication: stridor only.
Rapkin	..	Elective 5	.....	.....	..	..	..	The "observed and emergent tracheostomy" group was excluded from the total number.
Bass	..	Semielective 16	.....	.....	..	..	..	Also excluded those with emergency tracheostomy.
Palva	..	47	.....	.....	..	2	4	Series not all croup and epiglottitis deaths—1 emergency tracheostomy, 1 cannula (SGS).
Freeland	..	14	7 days	.....	..	..	..	Long follow-up with normal airway sizes.
Parton	..	26	5.8 days	.....	..	2	..	Both deaths—emergent tracheostomy.
Allen	61	.....	.....	.....	..	1	..	Reintubation required in 23. 33 had elective follow-up laryngoscopies (normal by 6 months) (30 by 3 months).
Margolis	..	15	<4 days	.....	..	..	..	.....
Milko	5	32	38 hours tube/ 7-day tracheos.	6.5 days tube/ 9-day tracheos.	..	..	..	.....
Geraci	2	.....	2 days	7 days	..	..	..	.....
Striker	11	.....	.....	.....	1	2	5	Airway complications: 3 subglottic stenoses, 2 granulomas. 4 of these required tracheostomies, 1 death—tube compression by edema.
Fearon	72	.....	.....	.....	..	..	11	Subglottic stenoses 6, 5 tracheostomies. 29 survivors—7 have laryngeal stenosis.
Fearon	..	336	.....	.....	2	2	..	2 deaths of disease only, 2 of tracheostomy complications (accidental extubation).
Schuller	86	.....	75 hours	.....	9	..	1	1 subglottic stenosis (1.6 percent).

Against tracheostomy are these arguments:

- Accidental decannulation is an emergency and may be fatal,
- Longer hospital stay,
- Surgical scar,
- Decannulation may be a problem (in fact, one of the techniques for accomplishing decannulation of a tracheostomy is the installation of a nasotracheal tube).[19]

Review of the Literature

In view of the existence of two effective forms of treatment for croup and epiglottitis, an attempt was made to survey both methods as to their efficacy and complications. A summary analysis was then done to determine if a trend existed in support of one treatment over the other.

Seven series of nasotracheal intubations were reviewed. Eight series reporting tracheostomies were reviewed. One report (Milko[15]) included both forms of treatment in the review. The following measures were evaluated:

- Average tube time,
- Average time in hospital,
- Deaths from airway obstruction,
- Airway complications following extubation.

As "observation and emergency tracheostomy" in epiglottitis has been previously shown to be dangerous, deaths from "emergency tracheostomy" were excluded from the series. This was done in order to prevent the occurrence of death from emergent tracheostomy from interfering with the comparison of long-term efficacy and complications of these two methods. The latter was the explicit purpose of this review. In addition, deaths due to septicemia, pneumonia and the like were also excluded from this summary (see Table 1), so that pure effects of intubation and tracheostomy could be compared.

Many of the reports cited did not include duration of the nasotracheal or tracheostomy intubation. Most series also lacked figures on hospital stay. One factor thought to be important in the production of laryngeal and tracheal stenosis is the size of the tube used. Information as to tube size also was lacking from all series reviewed.

Review Material

In all, 295 cases of nasotracheal intubation and 591 cases of tracheostomy were reviewed. In 151 cases for which average tube time was reported for nasotracheal intubation, an average of 2.8 days resulted. This compares favorably with average tube time for tracheostomy. A total of 72 cases were reported in series including average duration of indwelling tracheostomy tube. The average time for these tracheostomy patients was 6.2 days (see Table 2).

TABLE 2.—*Duration of Intubation*

	No. Cases	*Average Duration of Indwelling Tube*
Tracheostomy	72	6.2 days
Nasotracheal tube	151	2.8 days

TABLE 3.—*Length of Time in Hospital*

	No. Cases	*Average Days in Hospital*
Tracheostomy	32	9.0
Nasotracheal tube	61	7.1

Sixty-one intubated patients were included in reports citing average length of time in hospital. The average in this group was 7.1 days. The only report noting length of time in hospital for the patients in whom tracheostomy was done was that of Milko. In 32 patients reviewed, the average time in hospital was nine days (see Table 3).

Complications

The occurrence of accidental extubation and its sequelae in this report agrees with current thinking. In Battaglia's series of 34 nasotracheal intubated patients, accidental extubation occurred five times. In only one of these was an emergent reintubation required. In Striker's report there was one accidental extubation of the nasotracheal tube which proved fatal in a patient with a large oropharyngeal tumor. This, of course, was not included in the comparison of croup and epiglottitis patients. Allen did not report accidental extubations, but in 23 of his 61 patients reintubation had to be carried out.

In the series of 591 tracheostomies, there were two accidental extubations reported. Both of these resulted in fatalities.

Deaths from Airway Obstruction*

Allen reported one such death, and Striker also reported one fatality in the 126 patients reviewed having nasotracheal tubes for the treatment of croup and epiglottitis. This results in a mortality figure of 0.9 percent for nasotracheal intubation (see Table 4).

*Excluding the emergency tracheostomy.

TABLE 4.—*Deaths from Airway Obstruction (Emergency Tracheotomy Excluded)*

	No. Cases	*Deaths*
Tracheostomy	591	3 (.5%)
Nasotracheal tube	126	2 (.9%)

Palva reported one death from tracheostomy in a patient with an obstructed cannula. This patient was being treated for subglottic stenosis, but the report did not mention how this stenosis was incurred. Fearon's two patients died from accidental extubation, giving a total of three such fatalities in 591 tracheostomies done for croup and epiglottitis. This is a mortality incidence of 0.5 percent. The difference in these figures is not statistically significant and no inferences should be made.

Other Complications

The occurrence of subglottic stenosis is often cited as a reason for preferring tracheostomy to nasotracheal intubation. In the patients in whom nasotracheal intubation was done for croup and epiglottitis, there were reports of one patient with subglottic stenosis, two patients with subglottic granulation tissue and nine patients with "stridor only." In addition, Allen carried out direct laryngoscopy on 33 of his 61 patients having had nasotracheal tubes.[7] He found a normal airway in 30 patients after three months had elapsed, and in the other 3 a normal airway was present by six months. Striker used nasotracheal intubation for five patients with "croup following general anesthesia."[5] In three of these five subglottic stenosis developed, two requiring tracheostomy. A closer look at this article is in order.

Striker included reviews of 116 nasotracheal intubations. Only 11 intubations were done for croup and epiglottitis, and these were included in the group of 18. In four patients subglottic stenosis developed and subglottic granulomas developed in two others. A thin wall polyvinyl chloride tube was used for intubation. The tube size was not mentioned. The compressibility of this tube may have been responsible for one death in a patient in whom tube occlusion developed secondary to subglottic edema. Subglottic edema with "tube compression" occurred in two other patients, requiring tracheostomy in both. Striker stated "the tube acted as a foreign body which further irritated and inflamed the edematous mucosa." From these experiences, he concluded that nasotracheal intubation had no place in the treatment of obstructive upper airway disease in children. Similar findings were cited by Fearon in 1966 in his series of 72 intubations for other diseases.[6] (It is of course to be stressed that this is not a croup and epiglottitis series.) Of the patients in this series, 43 died of their diseases; 20 autopsies were done. In 11 of 43 patients who died, traumatic changes were found in the larynx and trachea at autopsy. In the 27 survivors, seven laryngeal stenoses occurred. One must be cautious in making inferences from these data. Certainly other influences are present such as sepsis, hypertension, hypoxia and other disease states which may lead to laryngeal and tracheal stenotic changes. Many investigators currently feel that use of oversized tubes and excessive tube movements are responsible for laryngeal and tracheal stenoses such as those cited above.[5-7]

Nonfatal Complications in Tracheostomy

Freeland's review of 14 tracheostomies cited a long follow-up with normal airway sizes. There were no subglottic stenoses or tracheal stenoses reported in the 591 reviewed herein.

Discussion

It is evident that physicians dealing with patients having croup and epiglottitis have two effective modes of therapy available. The drastic reduction in deaths and airway complications in all patients having croup and epiglottitis is ample evidence that both techniques are accepted and efficacious. It is up to the team of pediatricians, otolaryngologists and anesthesiologists in each hospital to determine the availability of proper nursing and paramedical care, as well as equipment, in deciding which method is preferred.

Certainly any surgeon carrying out pediatric tracheostomies is familiar with the necessity for constant attentive nursing care, frequent suctioning of tracheal secretions and continuous humidification of the inspired air. This is not to say that the technique of nasotracheal intubation requires any less care than does tracheostomy. Humidification, frequent suctioning and a meticulous method of securing the tube in place are all essential principles of this treatment. The two series cited in which nasotracheal tubes were left indwelling for long periods of time (Fearon,[5] Striker[6]) indicate that the passage of time does increase the complication rate when using this method. Other factors cited in the literature may be of more etiological importance. Movement of

the patient and the tube during artificial ventilation is one such factor. Probably even more important is the use of large nasotracheal tubes which can cause circumferential subglottic injury at the cricoid cartilage. This is felt by many to be *the* most common cause of subglottic stenosis from endotracheal tubes. Johnson has seen a case of subglottic stenosis in a patient having an indwelling endotracheal tube for only 24 hours.[21] Thus, there appear to be several factors important in the development of subglottic stenosis following endotracheal intubation.

The often quoted fear of abrasion and other injury of the inflamed supraglottis by an indwelling endotracheal tube was not borne out by any supraglottic webs or stenoses in the cases reviewed.

A regimen can be suggested that takes all these points into consideration: (1) If the epiglottis is red or inflamed, intubate immediately using a nasotracheal tube one size smaller than normal for the age of the patient. (2) For croup, intubate at the first sign of fatigue, restlessness, cyanosis, increased pulse or respiratory rate. (3) If complications ensue, assisted ventilation is necessary or long-term intubation becomes necessary, carry out tracheostomy.

When a tracheostomy becomes necessary, it should be done through a horizontal skin incision at the level of the second tracheal ring. Vertical dissection will avoid complications and should take the surgeon directly to the pretracheal fascia. The thyroid isthmus should always be divided if problematical by location. In the pediatric age group, a vertical tracheal incision should be made through the second and third rings. A 4-0 nylon suture passed through each side of the trachea lateral to the incision will facilitate insertion of the tube and recannulation if accidental extubation should occur.[22]

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Severe Iron Deficiency Anemia

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Severe iron deficiency anemia remains a continuing major health hazard among inner city children in Los Angeles. Over a 24-month period, 60 children in whom hemoglobin values were below 7 grams per dl were admitted to hospital; 11 (18 percent) of them were in overt congestive heart failure. Contrary to the popular conceptions, two thirds of the anemic children were undernourished, approximating the 16th percentile for weight on the Iowa growth chart, and the frequency of premature birth was not greater than in the general population. There were no deaths in this series. A management protocol which included partial exchange transfusion of children in congestive heart failure and supportive transfusion for children with hemoglobin levels below 5 grams per dl was employed.

SEVERE IRON DEFICIENCY ANEMIA is a distressingly common problem observed in children from disadvantaged socioeconomic populations in metropolitan Los Angeles despite all current efforts, including iron fortification of infant formulas. Patients at the Los Angeles County-University of Southern California (LAC-USC) Medical Center Pediatric Emergency Room were surveyed for anemia in 1966.[1] In a third of the children between the ages of 3 months and 24 months there were hemoglobin levels below 10 grams per dl (or hematocrit less than 30 percent). Subsequent intermittent screening procedures have shown no substantial decrease in the prevalence.

An analysis of pediatric mortality statistics for LAC-USC Medical Center for the years 1960-1970 showed there to have been 12 deaths in which severe iron deficiency anemia was felt to be the major contributory factor. This unexpectedly high number of deaths, associated with the constantly recurring clinical observation of seriously ill iron deficient children in the population served, prompted a detailed evaluation of 60 consecutive hospital admissions for severe iron deficiency anemia during a subsequent two-year period. The intent of this study was to identify those specific characteristics of these children that might contribute to a high risk of iron deficiency, to evaluate the current treatment methods and to underscore the persistence of severe, occasionally lethal, nutritional iron deficiency anemia in young children.

Characteristics of Iron Deficient Patients

The records of 60 consecutive patients admitted to hospital with the primary diagnosis of severe iron deficiency anemia during a two-year period were reviewed. Criteria for admission included all patients in whom hemoglobin concentrations were below 5 grams per dl, and all patients in whom

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ABBREVIATIONS USED IN TEXT

CHF = congestive heart failure
CPD = citrate phosphate dextrose
2,3 DPG = 2,3-diphosphoglycerate

hemoglobin concentrations were between 5 and 7 grams per dl complicated by a secondary illness. Of these 60 patients, 26 were male and 34 female. The racial distribution was 15 black, 35 Mexican-American, 7 Caucasian and 3 American-Indian. Mean age at the time of diagnosis was 14.2 months with a range of 5 to 56 months (Figure 1). No deaths related to this diagnosis occurred during the period of the review. Thirty-nine children (65 percent) were at or below the 16th percentile for height and weight (Iowa growth chart). These children appeared generally undernourished, a finding which differs from the commonly held belief that a child with iron deficiency anemia is a "fat milk baby." Newborn histories gave no evidence of major complications that might have predisposed to iron deficiency anemia. Of seven patients with birth weights less than 2,500 grams, the mean age at the time of diagnosis was 12.8 months, not significantly different from that of the entire group. Using immunization guidelines recommended by the American Academy of Pediatrics,[2] 37 patients (62 percent) had not been adequately immunized.

Table 1 summarizes the problems which prompted the arrival in our clinic. On several occasions more than one initial complaint was noted. The parents seldom sought the medical attention for pallor alone or for symptoms specifically related to the anemia. In the single patient presenting with the history of hematemesis, no source of gastrointestinal or pulmonary blood loss could be identified. A child presenting with traumatic amputation of a finger was found to have rickets and severe anemia. Anemia had been recognized previously in four children, although no treatment had been provided for three of these. Dietary management alone had been attempted unsuccessfully for an anemia of undetermined severity in the fourth, in whom the hemoglobin concentration was 2.9 grams per dl when admitted to hospital several months later. The diets of 45 patients (75 percent) were inadequate in nutritional iron content. Most diets consisted of whole milk to the virtual exclusion of other foods. An important feature of the nutritional history was the inconsistency of the dietary information during successive interviews. This may reflect a parental lack of knowledge of the child's dietary intake and disapproval implied by questions from medical personnel regarding the diet.

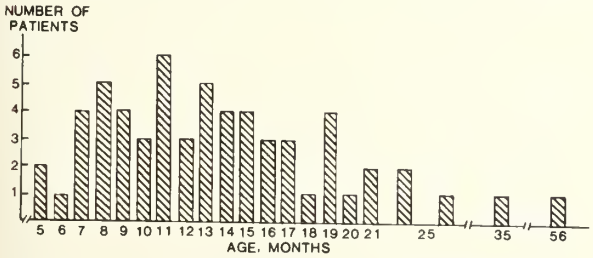

Figure 1.—Age distribution of 60 children admitted to hospital with iron deficiency anemia.

On physical examination it was found that 13 children had rectal temperatures greater than 38° C. Cardiac auscultation showed systolic murmurs in 45 cases. In 11 patients (18.3 percent) hepatomegaly was present and in 5 (8.3 percent) splenomegaly was found. The most frequently noted abnormalities on chest roentgenograms were cardiac enlargement seen in 11 patients and associated increased pulmonary vasculature in 6. Distinct pulmonary infiltrates were seen in five patients.

Electrocardiographic abnormalities were found in 12 patients, eight of whom were in congestive failure. Ventricular hypertrophy was the most frequent finding, appearing in ten patients, in one of whom there were associated significant Q waves. Of the remaining two patients, ST segment elevation was present in one and in the other there were signs of hypokalemia. Gastrointestinal blood loss was not shown by testing for occult blood in feces, although only one or two stool specimens generally were tested before therapy. Because the degree of the anemia required immediate attention, no effort was made to maintain high milk

TABLE 1.—*Presenting Complaints of 60 Children Admitted to Hospital with Iron Deficiency Anemia*

Upper respiratory tract infection	14
Pallor	8
Diarrhea and vomiting	6
Well baby care	6
Pulmonary infection	3
Convulsions	2
Epistaxis	1
Hematemesis	1
Skin infection	1
Adenopathy	1
Trauma	1
Incidental (brought with sibling)	1
Anemia identified by referring private physician	16
Anemia identified by referring public health nurse	2

intake in order to show there to be intermittent gastrointestinal bleeding. Absence of occult blood may have been due to immediate curtailment of excess milk intake or to the recognized sporadic appearance of blood in the stool.

Congestive heart failure (CHF) occurred in 11 of the 60 patients (18.3 percent). Of these, six presented with cough and rapid respiration and one with vomiting. The others were brought to medical attention for a variety of reasons including pallor, anorexia and weight loss. Remarkably, one child with CHF had appeared at the hospital for a well baby examination.

On physical examination of the patients in failure, tachycardia and systolic murmurs were seen in ten, gallop rhythm in three, hepatomegaly in nine and splenomegaly in three. In one child cardiac decompensation developed within 24 hours of admission to hospital.

Hematologic Diagnosis

All hemoglobin concentrations were less than 7 grams per dl and 42 (70 percent) were less than 5 grams per dl. In the children with congestive heart failure there generally were lower levels and in only one was the level greater than 5 grams per dl (Figure 2). Mean corpuscular hemoglobin concentration values ranged from 29 percent to 20 percent with a mean of 25 percent. Thrombocytopenia was present in 3 patients and thrombocytosis in 21; platelet counts did not correlate with severity of anemia.

Classic hypochromic microcytic morphology was present in all patients. When hemoglobin concentration was less than 5 grams per dl the extreme poikilocytosis and anisocytosis appeared similar morphologically to homozygous beta thalassemia, even when specific care was taken to minimize the artifact commonly produced in preparing blood films in severe anemia.

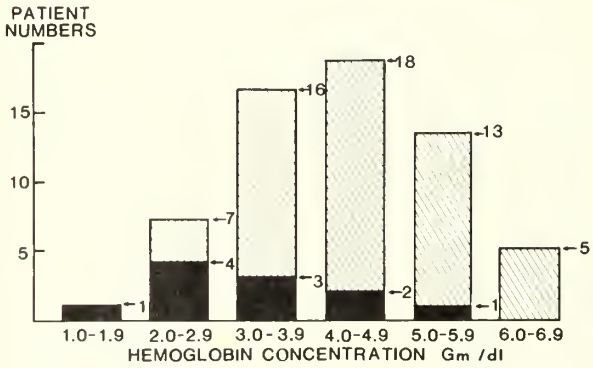

Figure 2.—Distribution of admission hemoglobin concentrations for the 60 patients in hospital. Solid portions represent patients in congestive heart failure.

Therapy consisted of packed red cell transfusion often as a partial exchange in each of the children in congestive heart failure. Transfusions were administered slowly with careful monitoring of heart and respiratory rate. Oxygen was administered until the child's condition was stable. No adverse effects of transfusion therapy were noted. Failure was reversed within three hours of the institution of therapy. Electrocardiographic and roentgenographic abnormalities when present returned to normal within 24 hours.

A total of 24 patients not in heart failure received transfusions as part of their therapy. Significant tachycardia (heart rate greater than 120 beats per minute) was present in 22 of these children, 15 of whom were afebrile. As with the children in failure, care was taken to administer the packed cells slowly. Partial exchange was seldom utilized in these cases. In no child treated in this manner did heart failure or other complications of the procedure develop.

In all, 25 patients were felt to be sufficiently stable to be treated with medicinal iron without transfusion. Orally given preparations were most frequently used although a child occasionally received an injectable iron preparation when the physician felt the parent was not likely to comply with oral therapy. Similarly those patients receiving transfusion as their initial treatment were given supplemental iron to replenish their deficient iron stores. Although used less frequently than in the nontransfused group, parenteral iron was administered to certain patients in whom compliance was felt unlikely.

During the stay in hospital an attempt was made to correct the poor dietary habits that led to the illness. If a child was 11 to 12 months or older, bottle feeding was curtailed and solid foods begun. Proper nutritional practices were discussed with the parents and referral to a public health nurse was made when additional education and support was felt necessary .

Return appointments were kept by only 40 of the 60 patients. Correction of the anemia was achieved in all who returned and no record of recurrent anemia was found in the hospital chart of any patient.

Mortality

Identification of 12 deaths over a ten-year period clearly attributable to the effects of nutritional

iron deficiency was made by computer-assisted retrieval of autopsy data, by a review of deaths in a program directed toward the postmortem diagnosis of sickle cell disease in black infants who died unexpectedly and by the personal records kept by one of us (D.P.). It is unlikely that these children represent all deaths related to iron deficiency anemia during this period since each identification procedure showed cases not contained in the other two. High output congestive heart failure was the ultimate cause of death for most of these children. Detailed information regarding some aspects of the laboratory and clinical course of their illness is not available but some salient features are apparent.

The 12 fatal cases were from 7 to 20 months of age and were equally distributed by sex. Racial distribution was eight blacks, three whites and one Mexican-American. Hemoglobin concentration on admission ranged from 1.3 to 6.9 grams per dl with a median value of 4 grams per dl. In seven of these fatal cases, the event initiating admission was overt respiratory distress and failure. None of the children had been brought to a health care facility regularly. Historical information regarding diet or immunizations was not obtained or was considered unreliable. Transfusions were initiated in three children. In the remaining nine, there was either insufficient time available or lack of clinical appreciation of the severity of the illness. Length of stay in hospital before death ranged from 0 to 28 hours. Postmortem examination was done on seven patients. The cause of death was due exclusively to congestive heart failure in six, of which in four there was autopsy evidence of severe fatty degeneration of the myocardium. This degree of cardiac involvement suggests that a therapeutic regimen aimed only at restoration of cardiac function (such as with digitalis) or rapid blood replacement which increases total blood volume would not be effective in preventing death. In the remaining six cases a variety of infectious illnesses were present in addition, including rubeola and interstitial pneumonitis.

Etiologic Factors

What is the role of poverty in the persistently high prevalence of iron deficiency anemia in this institution?

LAC-USC Medical Center is a major hospital serving the central area of the city of Los Angeles, and both referral and primary care are provided. The population is highly mobile and some are illegal aliens. Most patients are from low socioeconomic groups. The current ethnic distribution approximates 60 percent Mexican-American and 30 percent black.

Health care often is obtained only at times of crisis. Of all pediatric outpatient emergency visits, at least 50 percent are prompted by an acute infectious disease. Of the children seen in the pediatric emergency room at least 30 percent are from non-English speaking families. A minority of the staff physicians are bilingual, requiring the use of interpreters to provide communication between patient and doctor.

Of all patients seen in the pediatric outpatient department 12 percent are referred by private physicians, usually for a specific subspecialty evaluation. Another 7 percent are referred from public health clinics and 5 percent from various social agencies. Of the patients, 49 percent are self-referred on the advice of family or friends for treatment of acute illnesses. The remaining 27 percent use the institution as a source of primary care for all medical services, including fragmented well baby care.

Poverty and its related characteristics, lack of nutritional knowledge and fragmented medical care, probably represent contributing factors in the development of iron deficiency anemia. Feurth[3] noted a prevalence of anemia presumed to be due to iron deficiency of 3.6 to 6.3 per 100 in a predominantly middle class population while Hillman and Smith[4] reported 24 to 30 per 100 in the children of lower income urban families and Hutchinson[5] found at least 10 per 100 in rural poor children. Large families are common in disadvantaged populations and may create inordinate demands on the mother's ability to give proper nutritional supervision to each child. Conversely, young inexperienced mothers with limited family support are unlikely to understand basic infant nutrition.[6]

Overreliance on milk as a source of nutrition and the prolonged use of bottle feeding were the two most frequently discovered faulty dietary practices in this study. The use of iron-fortified foods and formulas has been thought to be a simple, effective way to provide adequate dietary intake of iron. The iron in fortfied formulas is absorbed readily. However, recent evidence indicates poor absorption of iron used to fortify infant cereals.[7]

Nutritional education currently may be delivered postnatally in hospital and at the time of the well baby visit. Unfortunately, a considerable

proportion of parents from low socioeconomic populations do not participate in this or other forms of preventive health care. This is indicated by the low rate of immunization that, in a previous study from this institution, was shown to be directly related to a high incidence of iron deficiency.[1] Disadvantaged mothers often receive insufficient professional feeding advice during their brief postpartum hospital stay. Furthermore, the mothers may be dismissed with written instructions that are far above their reading vocabulary level (hence incomprehensible) and several days' supply of 4-ounce bottles of prepared formula. The latter practice seems especially reprehensible since mothers can only infer that 4 ounces of milk is the correct amount to be given to a small infant at each feeding. Consequently, children are overfed on milk almost from the first day of life. If the parents can be convinced to wean a child after the ninth month or at least to limit the use of the bottle, the decreased intake of milk will allow the addition of foods with greater iron content.

The concordant finding that of the 60 anemic children 36 (60 percent) were inadequately immunized further emphasizes the urgent need for effective health education for inner city families.

Management

Transfusion

Congestive heart failure was the most frequently noted cause of death in the 12 children who died of iron deficiency anemia and was found in 11 of 60 (18.3 percent) of the patients in hospital. Very little published data exist regarding the actual cause of death of children who were thought to die with this disorder but it is generally felt that immediate treatment should be directed toward the prevention or reversal of heart failure.

Definitive therapy for CHF complicating severe anemia consists of red cell replacement. Rapid reversal of circulatory congestion can be achieved by an infusion, 2 ml per kg of body weight, of packed red cells concurrent with an equivalent volume phlebotomy.[8,9] This is followed by transfusion of additional red cells (10 ml per kg of body weight), at a rate of administration no greater than 5 ml per kg per hour. After eight hours, to allow cardiovascular equilibration, further transfusion may be given at the same rate to raise the hemoglobin to the desired level. Transfusion of large volumes of blood with low 2,3-diphosphoglycerate (2,3 DPG) concentration should be avoided to prevent tissue hypoxia from poor oxygen release.[10] In blood anticoagulated and stored in citrate phosphate dextrose (CPD) substantial blood replacement should be made with units no more than three days old.

The value of digoxin in the treatment of CHF in anemic children is uncertain.[11] Rapidly acting diuretics are useful adjuncts to transfusion therapy when pulmonary edema exists. Oxygen administration appears to be valuable. Although the oxygen saturation of hemoglobin approaches 100 percent at room air, a volume of oxygen can be dissolved in plasma in amounts that equal that carried by 1 gram per dl of hemoglobin. This represents a significant addition when extremely low hemoglobin levels are present and has been shown to favorably affect certain cardiovascular measurements in severely anemic children.[12]

Few data are available to provide an objective basis for recommendation concerning the level of anemia that should be used as an absolute indication for transfusion in children not in congestive heart failure. A hemoglobin concentration of 3 grams per dl in an otherwise well-appearing child, or 4 grams per dl in one who has an intercurrent illness has been shown to be associated with increased cardiac output at a level that is known to cause congestive heart failure.[13] Of our 42 patients in whom hemoglobin concentrations were less than 5 grams per dl, ten (24 percent) were in overt congestive failure at the time of hospital admission substantiating the significant risk of developing congestive heart failure below this hemoglobin level.

Iron Therapy

For those patients in whom hemoglobin concentrations were above 5 grams per dl and who were not in congestive heart failure, therapy was oral administration of elemental iron at 4 to 6 mg per kg per day until hemoglobin concentration returned to normal and for one month thereafter to replenish iron stores.

Certain indications exist for the use of injectable iron preparations. Some children may not tolerate orally given iron preparations well or parents may not comply adequately in administering the medication. Several methods have been suggested to increase parental compliance with therapy.[14] Effective communication of the importance of the medication is vital. While injectable iron avoids the problem of noncompliance, it also may avoid an important interaction between parent and doctor regarding necessary dietary changes.

Nutritional Education

Parental education in proper nutritional practices is an important facet of therapy of children with severe iron deficiency. Overreliance on milk as a source of nutrition and the prolonged use of bottle feeding were the two most frequently discovered faulty dietary practices in this study. An attempt should be made to outline a diet providing balanced nutrition and including sufficient iron. If parents can be convinced to wean a child or at least to limit the use of the bottle, the decreased intake of milk will allow the addition of foods with greater iron content.

Summary

Severe iron deficiency anemia resulted in admitting 60 children, 11 of whom were in congestive heart failure, to hospital. This points to the significance of this continuing major health hazard in economically deprived children.

It is unfortunate that an entirely preventable disease such as severe nutritional iron deficiency anemia continues to occur with such frequency as to engender this report. In view of the past experience which included 12 deaths, the lack of mortality at this institution during the past two years is encouraging but probably is related to increased proficiency in dealing with life-threatening emergencies rather than a decrease in incidence of severe cases.

In view of accumulating evidence[15] that ultimate adult intellectual attainment may be deleteriously affected by even minimal iron deficiency during the first three years of life, inadequate health education regarding infant nutrition among the inner city parents must have tragic consequences.

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Specialty Conference

Moderator

PHYLLIS A. OILL, MD

Discussants

JOHN Z. MONTGOMERIE, MD
WILLIAM S. CRYAN, MD
JOHN E. EDWARDS, JR., MD

This is a transcript of one of the regular Teaching Conferences in Infectious Diseases held weekly at Harbor General Hospital, Torrance, California. These conferences have been edited by Doctors Anthony W. Chow, Thomas T. Yoshikawa, Phyllis A. Oill and Lucien B. Guze.

Refer to: Oill PA, Montgomerie JZ, Cryan WS, et al: Infectious disease emergencies—Part V: Patients presenting with localized infections, *In* Infectious disease emergencies—Teaching Conference, University of California, Los Angeles, and Harbor General Hospital, Torrance (Specialty Conference). West J Med 126:196-208, Mar 1977

Infectious Disease Emergencies

PART V:

Patients Presenting with Localized Infections

PHYLLIS OILL, MD:* This is the fifth and final part of the symposium on Infectious Disease Emergencies. The discussions will deal with emergent and semi-emergent localized infections. First, Dr. Montgomerie will discuss soft tissue infections. The next discussant, Dr. William Cryan, will address himself to the topic of septic arthritis, and finally, Dr. John Edwards will discuss emergency eye infections.

Soft Tissue Infections

JOHN MONTGOMERIE, MD:† Inasmuch as this symposium deals with infectious diseases emergencies, only those serious and potentially life-threatening soft tissue infections will be discussed. Successful management of most of these infections depends on early diagnosis, usually by clinical signs alone. Table V-1 has been compiled to aid in the differential diagnosis of the first five soft tissue infections presented (clostridial myonecrosis, streptococcal and staphylococcal myositis, synergistic necrotizing cellulitis, necrotizing fasciitis, progressive bacterial synergistic gangrene). Salient features of decubitus ulcers with sepsis, human and animal bites, and serious furunculosis and cellulitis are also discussed.

Clostridial Myonecrosis (Gas Gangrene)

Clostridial myonecrosis or gas gangrene is a rapidly progressive infection associated with muscle necrosis, but relatively little inflammatory reaction. Although the highest prevalence of gas gangrene has been associated with war wounds, the disease also occurs in civilian practice following trauma, intraabdominal surgical procedures, especially cholecystectomy and intestinal resections, septic abortion and limb amputations. Patients with diabetes mellitus, certain types of neoplastic disease and disorders of the intestine in which there is appreciable necrosis of tissue are particularly predisposed to this infection.[1]

The etiologic agents are various histotoxic clostridia (Clostridium perfringens, C. novyi, C. septicum, C. histolyticum, C. bifermentans and C. fallax), with the most common pathogen being C. perfringens.[2] An individual lesion may yield more than one species. The toxins elabor-

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ABBREVIATIONS USED IN TEXT
GC = gonococcal
RA = rheumatoid arthritis

ated by these clostridia are, in part, responsible for the syndromes of gas gangrene.[2] Alpha toxin, a lecithinase, is the principal tissue-destroying, hemolytic and "lethal" toxin. Invasion of the blood stream by toxigenic clostridia rarely occurs as a complication of myonecrosis; however, in some patients, clostridial bacteremia leads to rapid and massive hemolysis as a result of the lecithinases.[1] Although the activities of some of the other toxins have also been defined, the precise cause of the systemic "toxicity" of this disease is still unclear.

The incubation period of gas gangrene is usually short, almost always less than three days and in most cases less than 24 hours.[2] The infection manifests itself with the sudden onset of pain in the region of the wound. The patient appears severely ill, pale and sweaty, and may be delirious, maniacal or apathetic.[1] Classically, there may be a peculiar period of great intellectual clarity, complete appreciation of the gravity of the circumstances, and a profound and distressing terror of impending death.[2] There is a pronounced rise in the pulse rate, but as a rule only a slight elevation in temperature, rarely to more than 100°F. After progression of signs and symptoms, a thin brownish exudate with a "mousey" odor begins to ooze from the wound. Crepitance may or may not be observed and gas is most easily detected on x-ray studies. It should be noted, however, that myositis may be present without gas. A bronze discoloration starts at the edge of the wound and progresses outward. Blebs or bullae filled with purplish fluid may appear, and by this time the patient may be anuric and in irreversible vascular collapse.[3]

Examination of the muscle by incision initially discloses only edema and pallor. As the infection progresses there is loss of contractility, absence of bleeding from the cut surface, and an increased reddening of the muscle from its normal color. Gas is present between the muscle fibers. Gram stain of the involved muscle shows large, Gram-positive or Gram-variable bacilli, but very few leukocytes.[3] Anaerobic cultures of this material should be sent to the laboratory for confirmation of the presence of clostridia. Smears of the superficial exudate from the wound may show a mixed bacterial flora due to contamination and may be misleading. Therefore, when gas gangrene is suspected, incision down to the muscle is necessary for direct observation, Gram stain and culture of muscle fibers.

TABLE V-1.—*Differential Diagnosis of Serious Soft Tissue Infections**

	Clostridial Myonecrosis	*Streptococcal Myositis*	*Synergistic Necrotizing Cellulitis*	*Necrotizing Fasciitis*	*Progressive Bacterial Synergistic Gangrene*
Incubation	18 hours to 3 days	3 to 4 days	3 to 14 days	1 to 4 days	10 to 14 days
Onset	Sudden	Gradual	Sudden	Sudden	Gradual
Toxemia	Marked	Marked after some time	Marked	Moderate to marked	Mild
Pain	Severe	Usually severe	Severe	Minimal; eventually hypoesthesia	Very marked
Exudate	Usually profuse, serosanguinous "mousey odor"	Very profuse, seropurulent	"Dishwater pus," foul smelling	Serosanguinous	Nil or slight
Gas	Rarely pronounced, except terminally	Present, not pronounced	Not pronounced, present in 25 percent of cases	Usually not present	Usually not present
Muscle	Edema, pallor to deep reddening; nonviable	Little change, but edema; viable	Moderate change, viable	Viable	No change
Skin	Tense, often white	Tense, often with coppery tinge	Discrete bluish-gray necrosis with areas of normal skin	Tense, pale red cellulitis	Fiery red cellulitis often purplish zone
Mortality	15 to 30 percent	5 to 10 percent	75 percent	30 percent	High

*Modified from Finegold SM, Bartlett, JG, Chow AW, et al: Management of anaerobic infections. Ann Intern Med 83:375-389, Sep 1975.

Additionally, the diagnosis of gas gangrene cannot be made simply by showing the presence of gas in tissues. A variety of other microorganisms (coliforms, anaerobic streptococci and bacteroides) may produce infections in which gas is shown present.[1] Crepitant cellulitis may be differentiated from gas gangrene by a more gradual onset of symptoms, a polymicrobial cause and involvement of epifascial soft tissues only.

Treatment must be prompt and vigorous, and complete surgical removal of all infected tissue is the only therapeutic modality proved to be unequivocally effective.[1,2,4] Antimicrobial therapy with penicillin G (10 to 20 million units per day in divided doses) is recommended to prevent blood stream invasion and to suppress further spread of infection. Chloramphenicol (4 grams per day in divided doses) is the alternative drug in penicillin-allergic patients. General supportive measures should include therapy with intravenously given fluids and blood, use of additional modalities to counteract the shock state and treatment with peritoneal dialysis or hemodialysis when renal failure is present. Hyperbaric oxygen has been advocated by some[5,6] as a dramatically successful mode of therapy that should even take precedence over immediate surgical management. The main advantage of hyperbaric oxygen therapy appears to be that it allows time for suitable medical resuscitation of the patient and better demarcation between necrotic and viable tissue before extensive surgical debridement is undertaken. If a suitable hyperbaric chamber is not locally available, it is probably unwise to delay surgical extirpation. The effectiveness of antitoxin therapy is unclear, but this should receive serious consideration when therapy with hyperbaric oxygen is not available.[1] The suggested dose of commercially available polyvalent antitoxin is 75,000 units given intravenously and repeated every six hours if necessary. Mortality in clostridial gas gangrene, despite vigorous therapy, ranges from 15 to 30 percent.[1,7]

Streptococcal and Staphylococcal Myositis

Streptococcal Myositis

This disease is characterized by severe local pain, generalized toxemia, discoloration, edema and crepitation of muscle.[8] It occurs in persons who have sustained traumatic wounds.

Streptococcol myositis may be due to anaerobic as well as aerobic streptococci (Streptococcus pyogenes, Streptococcus viridans), often in association with Staphylococcus aureus.[9]

The incubation period is approximately two to four days with a subacute or insidious onset. There is severe local pain with pronounced edema. A profuse, seropurulent discharge with a foul odor is generally present. There may be bleb formation and gangrene of the overlying skin. The skin is tense and can have a coppery tinge.[7] The muscle is edematous, but still viable and gas is apparent in the wound.[8]

The most important means of making the diagnosis is by direct examination of the muscle at operation. This is necessary in order to differentiate this disease from clostridial myonecrosis. This is usually possible by the more pronounced cutaneous reaction in the former, the discolored but still viable muscle, the foul odor and the presence of cocci on Gram stain of the fluid.[8]

Treatment requires incision and drainage of involved fascia and muscle groups. Concomittantly, antibiotic therapy is instituted with penicillin G (10 to 20 million units per day in divided doses) as the drug of choice. Mortality is 5 to 10 percent.[7]

Staphylococcal Myositis (Spontaneous Bacterial Myositis)

This is characterized by the spontaneous occurrence of abscesses in skeletal muscle. Pyogenic infection of skeletal muscle is rare in the West, but in the tropics it is one of the common outcomes of staphylococcal bacteremia.[10] The disease appears to have a predilection for children and adolescents, but it can occur in adults. Trauma and poor nutritional status are thought to be the predisposing factors in adults, but are not particularly significant in children.[10] Intravenous narcotic abuse has recently been associated with this complication.

Most cases of spontanteous bacterial myositis all over the world are caused by Staphylococcus aureus, although Staphylococcus albus and other organisms have occasionally been isolated.

The clinical features of this disease consist of localized muscle pain, followed in a few days by swelling, heat and tenderness, with or without fever and malaise. Local lymph nodes are usually not enlarged. Skin over the muscle abscess may be tight but is usually not edematous.[11] Blood cultures are generally negative by the time myositis occurs. The commonest site for pyomyositis is the thigh,[11] with buttock, arm, leg and groin

next.[10] Single abscesses are more frequent than multiple abscesses.

Treatment of spontaneous bacterial myositis includes surgical incision and drainage plus an appropriate parenteral antistaphylococcal antibiotic (methicillin, cephalothin). The mortality is low (approximately 1.4 per cent) but the condition can be fulminating.[11]

Synergistic Necrotizing Cellulitis

This disease is an aggressive soft tissue infection recently characterized by Stone and Martin.[12] The infectious process causes extensive necrosis of entire muscle compartments with little damage to the overlying skin and subcutaneous tissues and has associated severe systemic toxicity. There is a predilection for middle-aged and elderly persons in whom diabetes, renal disease and either obesity or malnutrition are present.

The disease results from a synergistic infection by one or more species of aerobic Gram-negative bacteria (Klebsiella, Enterobacter, Proteus mirabilis, Escherichia coli) and an anaerobe (anaerobic Streptococcus or Bacteroides or both).[12] It appears essential for both aerobic and anaerobic pathogens to be present for this extensive and rapid infection to occur.

The onset is acute and the incubation is variable, from three to 14 days. The infection is located primarily in the perineal area and the lower extremity. There are small skin ulcers draining copiously thin, reddish-brown, foul-smelling fluid referred to as "dishwater pus." There is exquisite local tenderness. The unique characteristic of this infection is discrete large skin areas of bluish-gray necrosis separated by areas of normal skin.[8] Some patients (25 percent) may have gaseous emphysema of adjacent tissues. Patients appear to be in a toxic condition although not all will be febrile. Uremia, anemia and ketoacidosis may be concommitant findings.

Diagnosis is made by doing a Gram stain of the exudate and identifying both Gram-positive cocci and Gram-negative rods. Blood specimens and the wound should be cultured both aerobically and anaerobically. There is a high incidence of associated aerobic and anaerobic bacteremia (30 percent).[12]

Therapy consists of radical surgical debridement and drainage in association with antibiotics to cover anaerobes (including B. fragilis) and bacillary Gram-negative aerobes. Clindamycin (600 mg given intravenously every six hours) and gentamicin (3 mg per kg of body weight per day in divided doses) are the antibiotics of choice. General supportive measures such as intravenous administration of fluids; correction of anemia, hyperglycemia and acidosis, and treatment of renal insufficiency are necessary. Mortality in this disease is high (75 percent).[12]

Necrotizing Fasciitis

Necrotizing fasciitis is a relatively rare, aggressive infection variably referred to as hemolytic streptococcal gangrene[13] and "hospital gangrene" in the older literature. The most significant manifestation of this infection is extensive necrosis of the superficial fascia with resultant widespread undermining of surrounding tissue and extreme systemic toxicity. Most cases occur following minor trauma or surgical procedures of the abdomen.[14,15] The highest incidence is seen in patients with ischemic small vessel disease, such as diabetes,[7] but it has also been noted in patients with neuropathies, urethral stricture, cirrhosis and heroin addiction.[16]

It was originally believed that aerobic organisms, particularly the hemolytic streptococci and staphylococci and Gram-negative bacilli, were the primary pathogens responsible for this infection.[13-15,17] However, with careful bacteriologic techniques the cause consistently has been shown to be polymicrobial, involving both anaerobes and aerobes.[16] The predominant anaerobes include Peptostreptococcus, Bacteroides, and Fusobacterium; the predominant aerobes include Escherichia coli, Proteus, Staphylococcus and Streptococcus.[16]

The disease is characterized by a rapid course. Initially there is pain (minimal) and swelling at the site of injury and the involved site becomes red, hot, swollen and edematous. Subsequently, there is hypoesthesia about the wound. The patient has a rapidly developing fever which may be preceded by a chill and is almost always followed by prostration.[13] The early swelling makes the skin tense, smooth and shiny with no sharp line of demarcation between normal and affected skin. As the disease progresses, there is a dusky discoloration of the skin appearing as small purplish patches with irregular or ill-defined borders.[14] At this time blisters or bullae appear in the affected area, and widespread echymoses and necrosis of the skin can occur. Sometimes the area of skin necrosis is very small, while the subcutaneous gangrene is quite extensive.[13] Pro-

nounced apathy and weakness develop in the patient. Hypocalcemia, due to extensive subcutaneous fat necrosis, anemia and jaundice may develop.[8,15] Blood is lost from the general circulation in venous thrombosis and cutaneous hyperemia, and there is sequestration of large quantities of extracellular fluid in the acutely inflamed areas. Lymphangitis or lymphadenopathy (or both) is very rare in this condition.[13]

Diagnosis is made by having a high index of suspicion and evidence of extensive subcutaneous and fascial necrosis with undermining of skin.[17] If there is an opening in the skin, a hemostat or probe may be readily passed through the opening along the fascial plane. In cellulitis or erysipelas without necrotic fascia, an instrument will not follow the subcutaneous plane.

The initial management should consist of correction of fluid and electrolyte abnormalities, blood transfusions as necessary, blood and wound cultures (aerobic and anaerobic) and Gram stain of the wound exudate. Intravenous administration of antibiotics should be started immediately after cultures are obtained and should be directed against potential pathogens depending on the site of infection and findings on Gram stain of the wound exudate. For cases secondary to surgical operation of the abdomen or rectum where mixed aerobic and anaerobic pathogens including Bacteroides fragilis are common, a combination of gentamicin and clindamycin or chloramphenicol is recommended.[7] It must be noted, however, that the primary treatment is prompt, extensive surgical incision, debridement and drainage of the affected areas. It is only through the use of surgical procedures that mortality of this devastating infection (approximately 30 percent) can be decreased.[15]

Progressive Bacterial Synergistic Gangrene

This disease produces a progressive spreading ulceration and necrosis of the skin and subcutaneous tissues, and usually results as a complication of intraabdominal surgical procedures.[18] It is a synergistic infection most commonly caused by a combination of anaerobic cocci and aerobic Gram-positive cocci or Gram-negative rods. This infection is also known as Meleney's synergistic gangrene.[19]

The progress of this infection is not rapid and is not associated with high fever or toxemia usually seen with other grave soft tissue infections. The infection is typically recognized at 10 to 14 days after the initial injury or operation and often starts around the suture line. The process may best be described as a slowly advancing, white subcutaneous slough.[18] The skin surrounding the wound becomes edematous, red and usually tender. With progression, a characteristic lesion results that is demarcated into three zones. There is a peripheral wide area of fiery red cellulitis around a zone of purplish tender skin. The central zone becomes necrotic and will ultimately ulcerate. The central ulceration results in undermining of the skin edges of the circumscribed lesion.[8] The most distressing symptom is the acute sensitivity of the wound, making dressing and all manipulations about the lesion extremely painful.

Gram stain of tissue sections or subcutaneous aspiration may show the causative organisms and guide the appropriate choice of initial antimicrobial therapy. Aerobic and anaerobic blood and wound cultures should be routinely obtained for microbial confirmation.

Surgical drainage and debridement (often of large areas) is the major treatment modality; however, antibiotics assume a primary role before surgical intervention. Antibiotics given at first should cover both aerobic Streptococcus and Staphylococcus. High dose penicillin and methicillin should be administered parenterally. If Gram-negative rods are seen on Gram stain, gentamicin and clindamycin or chloramphenicol should be used. The mortality rate from this infection continues to be high owing principally to delays in diagnosis and therapy.[2]

Decubitus Ulcers with Sepsis

Decubitus ulcers result from local ischemic lesions caused by prolonged compression of tissue with subsequent necrosis. Patients who are bedridden, for whatever cause, are prone to decubitus ulcers. Under-nutrition, low serum albumin, anemia and circulatory impairment add seriously to the hazard of this complication developing.[20]

A multitude of organisms (aerobic and anaerobic) have been isolated from infected decubitus ulcers. The aerobic organisms producing sepsis include Proteus, Escherichia coli, Enterobacter, Pseudomonas aeruginosa, Staphylococcus, Streptococcus, diphtheroids and yeast. Anaerobic isolates include Bacteroides (especially B. fragilis), Fusobacterium, Peptococcus, Peptostreptococcus, microaerophilic Streptococcus, Clostridium and

Eubacterium.[21-23] Of importance, is the evidence that bacteremia is frequently associated with infected decubitis ulcers and is commonly polymicrobial with a predominance of obligate anaerobes, particularly B. fragilis.[21-23]

In the serious form, patients present with fever, chills, hypotension and tachycardia or tachypnea, or both.[23] There is extensive tissue destruction with necrosis. Lesions may be foul-smelling with purulent drainage. Lesions are usually more extensive than physical findings would suggest and associated osteomyelitis is a common finding (40 percent).[23]

Gram stain of the exudate is not particularly helpful since a polymicrobial smear is expected. Cultures of the decubitus ulcer and blood (aerobic and anaerobic) are essential.

Management entails careful evaluation of the patient's condition and consideration of the decubitus ulcer as the source of sepsis. The most important treatment with this disease is surgical debridement. Initial antibiotic therapy should include either clindamycin or chloramphenicol for coverage of anaerobic bacteria, particularly Bacteroides fragilis. In addition, an aminoglycoside, such as gentamicin, should be administered to provide coverage for coliform organisms. General supportive measures, such as fluids given intravenously and vasopressor agents, are indicated. Mortality in this disease is high (48 percent).[23]

Human and Animal Bites

Infection following human or animal bites is common. Infection in human bites is almost always polymicrobial and usually consists of the endogenous oral flora (both aerobes and anaerobes). Pasteurella multocida is commonly isolated following domestic animal bites[24] and may be associated with septicemia, especially in cirrhotic patients.[25] Streptobacillus moniliformis and Spirillum minus are the two organisms implicated in rat bite fever.[26] All of the above organisms are sensitive to penicillin which is the drug of choice for infection secondary to a bite. In addition, excision of the wound, copious irrigation with sterile saline and immobilization are necessary for complete management.[8] In only rare instances should bite lesions be sutured.

Furunculosis and Cellulitis

Furunculosis or boils due to S. aureus, and impetigo and cellulitis due to S. aureus or group A streptococci are rarely emergency problems. However, there are at least three situations in which these infections may be potentially life-threatening: (1) infection around the face, (2) cellulitis in the presence of peripheral edema which renders the infection rapidly progressive and more difficult to treat and (3) local infection in the presence of immune deficiencies, especially leukopenia or leukemia.

When the infection is around the face, there is a risk of cavernous sinus thrombosis. Cavernous sinus thrombosis most frequently follows a nasal furuncle, but may occur with infection of the sinuses, teeth, eyes or ears. Cavernous sinus thrombosis should be considered in the differential diagnosis of any patient with periorbital edema. Important features to distinguish it from orbital cellulitis are involvement of the 3rd, 4th, 5th and 6th cranial nerves with a dilated pupil and fullness of retinal veins. Bacteremia will be present and meningitis may also develop. A history of manipulation of the nose, squeezing it, extracting hairs from it or incising furuncles around it is obtained in approximately a third of patients with cavernous sinus thrombosis.[27] Because of this, incising furuncles on the face has not been advised.[27] If drainage of lesions on the face is important, it is recommended that antibiotic therapy be instituted for 24 to 48 hours before the incision. Antibiotic therapy before incision may also be important in patients with immune deficiencies.

In patients with cellulitis it may be very difficult to obtain the responsible organism. Injection of sterile saline followed by needle aspiration at the edge of the lesion for appropriate culture may aid considerably in recovery of the causative pathogen.[28] Blood cultures should also be done. Because S. aureus and group A streptococci are the most likely pathogens, initial antimicrobial therapy to cover both these organisms is recommended until culture results are available. Penicillin is still the agent of choice for streptococci, while semisynthetic penicillins, such as methicillin, or cephalothin should be administered for staphylococcal disease.

Septic Arthritis

WILLIAM S. CRYAN, MD:* Infection of the joint space represents a medical emergency. Physicians evaluating patients who present with monoarticular arthritis must entertain a complete differential diagnosis that includes trauma, gout, pseudo-

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TABLE V-2.—*Septic Arthritis*

Predisposing Factors
Antecedent joint disease
Old age and debilitation
Steroids or immunosuppressive therapy
Diabetes, malignancy
Recent arthrocentesis
Gonococcal disease
Other Clues to Diagnosis
Shaking chills, leukocytosis, fever
Often monoarticular although gonorrhea may be initially migratory
Pronounced signs of inflammation

gout, hemarthrosis, intermittent hydroarthrosis and a variety of less common conditions. There is a primary responsibility, however, to rule out infection as a cause. Septic arthritis may have tragic consequences, resulting in lifelong loss of joint function. As an example, staphylococcal arthritis, if untreated, can lead to destruction and loss of function of a joint in a few days. Early diagnosis is of cardinal concern because this is, in the main, a curable disease.

The predisposing factors and other clues to diagnosis of septic arthritis are listed in Table V-2. The normal joint has a relatively high level of integrity, and spontaneous infection is the exception rather than the rule. In persons with altered host defense mechanisms, one sees an increased frequency of septic arthritis. This is particularly the case in a patient whose altered defense mechanisms are related to abnormal joint space integrity. It has been recognized now for a number of years that in patients with underlying joint disease, such as rheumatoid arthritis (RA), there is a pronounced increase in the frequency of infection in the already damaged joints.[29] What is unfortunate is that septic arthritis in such patients is frequently overlooked as simply another manifestation of RA.

This phenomenon can be shown simply in the following experimental model. If one injects Escherichia coli or other organisms into the blood stream of a rabbit, inducing a bacteremia, septic arthritis does not ensue, proving the general integrity of the joint space. However, a septic joint will develop if injection of the same concentration of bacteria into the rabbit's bloodstream is followed by traumatization of the joint (such as puncturing the joint with a sterile needle). Similarly a prosthetic device in the joint is a predisposing factor for development of septic arthritis.

It would also appear that generalized host resistance is important. For example, the debility of aged patients, the presence of an underlying malignancy, the use of immunosuppressive agents or the presence of certain unrelated systemic illnesses, such as sickle cell disease, may all increase the possibility of septic arthritis developing. In addition, a vigorous search should be made to locate any extra-articular infective focus that may be a potential source for bacteremia. As an illustration, in a patient in whom intermittent episodes of bacteremia occur, as in a person with active bacterial endocarditis, the chances of infective arthritis developing are increased.

Another underlying factor to consider is the sociologic milieu of the patient. Certainly those persons in their sexually active years are at greater risk than others to develop gonococcal (GC) arthritis. Similarly, a person addicted to intravenously taken drugs is subject to an increased frequency of septic arthritis, often in unusual sites with uncommon organisms.[30]

Although most infected joints result from blood-borne infection, direct involvement of a joint with a septic process may occur. This is seen in patients in whom there is interruption of the joint space integrity consequent to trauma, direct spread of infection from adjacent osteomyelitis or local extension to the sacroiliac or hip joints, such as seen in patients with inflammatory bowel disease.[31]

Synovial fluid analysis is strongly indicated in any patient with monoarticular or unexplained pauciarticular disease. The evaluation of the joint fluid can be of prime importance in the differential diagnosis of the arthritic disorder. Gross examination and a few simple laboratory tests can help characterize the fluid into three main groups as noted in Table V-3. Once the grouping of the fluid is established, the differential diagnosis will be narrowed considerably (see Table V-4). The immediate aim is to differentiate an infected joint from the other possible causes of monoarticular or pauciarticular arthritis.

The diagnosis of septic arthritis is somewhat more difficult when the less common joints are involved. Infections of the sternoclavicular or sternomandibular joints in users of intravenously taken drugs[30] and a septic hip joint in a patient with inflammatory bowel disease[31] are illustrative of this point. As an aside, a patient with a septic hip may present with a complaint of knee pain,

for in such cases pain is referred to the knee via the obdurator nerve. In these instances examination of the "affected" knee may be unrevealing and only a subtle swelling in the inguinal region may be noted. Joint aspiration under fluoroscopy may be necessary to confirm the diagnosis.

The types of organisms that may cause septic arthritis are varied. The frequency of specific organisms differs according to the patient population studied and the geographic area. Although almost any microorganism can cause infectious arthritis, the common bacterial agents are listed in Table V-5.

In general terms, children are somewhat prone to pyogenic infection and approximately 40 percent of septic arthritides in children are due to Staphylococcus aureus with pyogenic streptococcus causing about 25 percent. In infants from 7 months to 4 years old, Hemophilus influenzae is being increasingly recognized as a common etiological agent[32] and is probably as common as S. aureus. Gram-negative infection with coliforms accounts for 15 percent of such cases. Although Neisseria gonorrhoeae has been reported in children under ten years of age, it is distinctly uncommon.

In adult patients, there is a shift in the statistics, predominantly because of the notably higher incidence of GC arthritis.[33] In many series N. gonorrhoeae is the etiologic agent in greater than 50 percent of patients with septic arthritis. S. aureus (25 percent), pneumococcus, streptococcus and Gram-negative bacilli are then seen in roughly that order.

Although excellent reviews of gonococcal infections have been published,[33,34] a brief characterization of GC arthritis will be presented since it is such a common form of septic arthritis in adults. Somewhat greater than 80 percent of cases are seen in women, about half of whom are pregnant, menstruating or in the immediate postpartum period.[34] It is, in the main, a complication of

TABLE V-3.—*Differential Diagnosis by Joint Fluid Groups**

Group I (Noninflammatory)	*Group II (Inflammatory)*	*Group III (Septic)*	*Hemorrhagic*
Degenerative joint disease	Rheumatoid arthritis	Bacterial infections	Hemophilia or other hemorrhagic diathesis
Trauma†	Acute crystal-induced synovitis (gout and pseudogout)		Trauma with or without fracture
Osteochondritis dissecans	Reiter's syndrome		Neuropathic arthropathy
Osteochondromatosis	Ankylosing spondylitis		Pigmented villonodular synovitis
Neuropathic arthropathy†	Psoriatic arthritis		Synovioma
Subsiding or early inflammation	Arthritis accompanying ulcerative colitis and regional enteritis		Hemangioma and other benign neoplasm
Hypertrophic osteoarthropathy‡	Rheumatic fever‡		
Pigmented villonodular synovitis†	Systemic lupus erythematosus‡		
	Progressive systemic sclerosis (scleroderma)‡		

*From Rodnan GP, McEwen C, Wallace SL (Eds): Primer on the rheumatic diseases. JAMA 224:661-812(Suppl), Apr 30, 1973, Copyright 1973, American Medical Association.

†May be hemorrhagic.

‡Groups I or II.

TABLE V-4.—*Examination of Joint Fluid**

Measure	*Normal*	*Group I (Noninflammatory)*	*Group II (Inflammatory)*	*Group III Septic*
Volume (ml) (knee)	<3.5	Often >3.5	Often >3.5	Often >3.5
Clarity	Transparent	Transparent	Translucent-opaque	Opaque
Color	Clear	Yellow	Yellow to opalescent	Yellow to green
Viscosity	High	High	Low	Variable
WBC (per cu mm)	<200	200-2,000	2,000-100,000	>100,000†
Polymorphonuclear leukocytes	<25%	<25%	50% or more	75% or more†
Culture	Negative	Negative	Negative	Often positive
Mucin clot	Firm	Firm	Friable	Friable
Glucose (mg/100 ml)	Nearly equal to blood	Nearly equal to blood	>25, lower than blood	<25, much lower than blood

*From Rodnan GP, McEwen C, Wallace SL (Eds): Primer on the rheumatic diseases. JAMA 224:661-812(Suppl), Apr 30, 1973, Copyright 1973, American Medical Association.

†Lower with infections caused by partially treated or by low virulence organisms.

genital tract infection. The interval from onset of genitourinary infection to arthritis is extremely variable; however, the most common length of time between contact and symptoms is approximately one week. Frequently the onset of the disease is heralded by fever (in 80 percent) and in some circumstances with chills. Migratory arthralgias will then occur with variable signs of articular inflammation. It is during this early bacteremic phase that skin lesions are most commonly seen and occur in up to 50 percent of patients. Tenosynovitis of the wrist is a common concomitant finding. Classically, during the bacteremic stage, blood cultures may be positive, but if joint fluid is obtained it may be negative. A day or two later frank purulent arthritis develops in the same joint and class III joint fluid will be obtained. Culture of this fluid is often positive for the organism. The knees are most commonly involved, with ankles and wrists following.

In cases of suspected GC sepsis, it is wise to culture the pharynx and anus as well as genitalia, blood and synovial fluid. Other laboratory modalities tend to be of variable value, with about 60 percent of patients showing leukocytosis. Recently the use of fluorescent techniques has been reported in an attempt to show the presence of gonococcal antibodies, but these modalities are not yet in general use.

Septic arthritis with a pyogenic organism (other than GC) may cause rapid destruction of a joint.[35] Pyogenic arthritis tends not to be associated with migratory arthralgias, although fever and chills are not uncommon. The onset may be quite explosive, with the patient presenting with an exquisitely tender, red, swollen joint. Changes on x-ray studies may occur in a matter of days, with soft tissue swelling and patchy areas of osteoporosis appearing as a consequence of the intense hyperemia.

Infectious agents other than bacteria (see Table V-6) can produce a septic joint, and some of these present in a more insidious manner. Chief among these would be tuberculous arthritis.[36] The classic presentation of articular tuberculosis is a monoarthritis of subacute onset with pain, swelling and limitation of movement. Often the disease is seen in boys with the major weight bearing joints affected: the spine, hips and small bones of the feet. Often there are associated tuberculous lesions of other organs, such as pulmonary, genitourinary and so forth. Soft tissue swelling may be the only finding on an x-ray study but eventually the characteristic articular and cystic changes will be seen. Later, gross active destruction of bone occurs as is generally the case with other septic lesions of joints. There tends to be greater involvement of the distal bony structures. This is in contradistinction to the inflammatory arthritides, such as RA, in which proximal involvement is greater than distal. Cultures of synovial fluid for Mycobacterium tuberculosis may be negative and definitive diagnosis is best achieved through synovial biopsy. In the vertebral column there is a propensity for involvement in the thoracic area.[37,38] With characteristic paravertebral abscesses, the "steering wheel sign" is seen on x-ray studies, the ribs seeming to radiate out from a hub. The infective process involves the vertebral body above and below the joint space. This is different from metastatic disease due to cancer which initiates in the vertebral body and thus spares the vertebral body either above or below the lesion. Anterior collapse of the vertebral body may occur, leading to the classic gibbus deformity seen with Pott's disease. Antituberculous therapy with two drugs (that is, isoniazid and ethambutol) is indicated for this disease.

As has been mentioned, it is extremely important to make an early diagnosis of an infective arthritis. In general, it is best to admit such patients to hospital for a course of parenteral

TABLE V-5.—*Bacterial Organisms Causing Septic Arthritis*

Neisseria gonorrhoeae
Staphylococcus aureus
Hemophilus influenzae
Pneumococcus
Streptococcus
Bacteroides
Escherichia coli
Pseudomonas aeruginosa
Others

TABLE V-6.—*Infectious Arthritis*

Bacterial (pyogenic)
Viral
Rubella
After rubella vaccination
Mumps
Infectious hepatitis
Other
Tuberculous
Fungal
Mycoplasma
Syphilitic

antibiotics. Most antibiotic concentrations in the serum will be quickly reflected in the joint fluid and intraarticular installation of antibiotics is generally unnecessary. However, it is useful to repeat arthrocentesis in such patients because accumulation of leukocytes and debris in such a joint may continue to cause destruction. Therefore, repeated arthrocenteses are therapeutic. It is infrequently necessary to carry out orthopedic or open drainage of joints because it has been found that there is no functional improvement when open drainage of joints is done in contrast to medical needle aspirations.[39]

Antibiotic therapy is directed toward the specific suspected organism. In the patient with S. aureus, it is generally recommended that nafcillin (25 mg per kg of body weight every six hours) or methicillin (6 to 8 grams per day in divided doses) be employed. If antibiotic sensitivities show that the organism is penicillin-sensitive, then penicillin G at 50,000 to 70,000 units per kg of body weight every six hours should suffice. Continued therapy using oral administration for an additional four to six weeks may be required when S. aureus is the organism. For N. gonorrhoeae, penicillin G is the drug of choice at 5 to 10 million units per day given intravenously in divided doses. In younger patients, where Hemophilus influenzae may be involved, one can substitute ampicillin at 50 mg per kg of body weight every six hours. If a Gram-negative organism is suggested, then gentamicin (3 to 5 mg per kg body weight per day in divided doses) should be given until culture results are obtained.

Emergency Eye Infections

JOHN E. EDWARDS, JR., MD:* Almost any infection of the eye is a relative emergency. However, this discussion will be limited to six entities which have been chosen from the perspective of nonophthalmologists. This selection may differ somewhat from the choice of general ophthalmologists. For instance, mucormycosis (phycomycosis) is included, which is of particular significance to internists but is infrequently encountered by general ophthalmologists. The first three entities, acute bacterial conjunctivitis, dacrocystitis and corneal ulcer are usually definitively diagnosed and treated by ophthalmologists, but may present initially to a primary physician in the emergency department. The last three infections, orbital cellulitis, mucormycosis, and endophthalmitis, frequently involve the combined efforts of an opthalmologist and an internist for both diagnosis and systemic therapy. Before discussing these entities in detail, the normal flora of the eye will be reviewed.

Locatcher-Khorazo and Seegal[40] have summarized numerous studies of normal eye flora which show the most common organisms cultured from uninfected eyes to be Staphylococcus aureus, Staphylococcus epidermidis and diphtheroids. A small percentage of normal patients harbor Gram-negative rods, including Pseudomonas aeruginosa. The presence of these Gram-negative rods should alert a physician to the necessity of giving adequate antibiotic coverage for these organisms when it is necessary to begin treatment for a severe infection without a specific diagnosis.

Fortunately, numerous antibiotics are capable of penetrating the eyes. Leopold and Kagan[41] have summarized these data and formulated a table outlining the potential for penetration into eye structures (see Table V-7). The routes for administration of antibiotics in eye infections include topical, subconjunctival, sub-Tenon and parenteral. The different clinical situations dictate the desired route of administration and will be discussed below.

Acute Bacterial Conjunctivitis

The clinical diagnosis of acute conjunctivitis usually does not create a diagnostic dilemma; however, one must not overlook an underlying panophthalmitis, associated orbital cellulitis, ocular trauma, foreign body or other primary intraocular processes. Locatcher-Khorazo and co-workers[42] reviewed the microbiology of 8,068 cases of acute bacterial conjunctivitis seen at the Institute of Ophthalmology, Columbia-Presbyterian Medical Center, between 1938 and 1968. In adults, Streptococcus pneumoniae, Hemophilus influenzae and S. aureus were the most common organisms. In children (up to 18 years old) S. pneumoniae and H. influenzae were still the most common organisms, followed by Streptococcus viridans and S. aureus. As expected, Neisseria gonorrhoeae played an important role in term babies. With the rising incidence of gonorrhea infections in this country, this organism should be kept relatively high in the differential diagnosis. Some cases have now been re-

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TABLE V-7.—*Intraocular Penetration of Antibiotics**

Relatively Good	*Fair*	*Poor*
Ampicillin	Colistin	Amphotericin
Cephalexin	Erythromycin	Novobiocin
Cephaloridine	Gentamicin	Oxacillin
Cephalothin	Kanamycin	Ristocetin
Chloramphenical	Methicillin	Streptomycin
Dicloxacillin	Neomycin	Tetracycline
Lincomycin	Oleandomycin	
	Penicillin	
	Polymyxin	
	Vancomycin	

Note: Those antibiotics with fair penetration are able to penetrate the inflamed eye in therapeutic concentrations against many organisms.

*From Leopold IH, Kagan JM: Antimicrobial therapy in ophthalmology, chap 40, *In* Kagan BS (Ed): Antimicrobial Therapy, 2nd Ed. Philadephia, W. B. Saunders Co., 1974, p 371

ported in association with disseminated gonorrhea in adults.[43]

Generally, it is possible to identify the specific agent by Gram stain and culture of the involved area. A swab of the infected conjunctiva will obtain appropriate material. Treatment is usually successful with a topical antibiotic (either sulfonamide or tetracycline). Although agents containing neomycin and polymyxin have been popular for years, recent evidence suggests that a significant percentage of pneumococcal organisms may be relatively resistant to these constituents.[44]

Acute Dacrocystitis

This disease is an inflammation of the nasal lacrimal ducts. By far the most common etiological agent is S. aureus, with S. pneumoniae second.[42] Nocardia is another organism that, surprisingly, has been frequently cultured from this infection and should be kept in the differential diagnosis. The most common complication of dacrocystitis is pneumococcal corneal ulcers. Optimal therapy consists of parenteral antistaphylococcal antibiotics and warm compresses. Additionally, this infection is almost always associated with obstruction of the lacrimal duct, which must be relieved to assure adequate healing.

Corneal Ulcers

When present in the relatively advanced stage, a corneal ulcer can be easily diagnosed by nonophthalmologists without the aid of specialized instrumentation. The definitive microbial diagnosis, however, is usually made by smear and culture of the base of the ulcer. The scraping of the ulcer base is best done by an experienced ophthalmologist. S. aureus, S. pneumoniae and P. aeruginosa are the most common organisms.[42] With the possible exception of the herpetic corneal ulcer, which has a dendritic configuration, one cannot make a clinical distinction between ulcers caused by other microbial agents.

The usual mode of treatment of the corneal ulcer is topical antibiotics. However, if there is extensive clouding of the cornea and anterior chamber inflammation suggestive of intraocular penetration, systemic antibiotics are required in addition. Because of the relatively high incidence of Pseudomonas and its potential for aggressive destruction (it may cause loss of the eye in 48 hours), appropriate coverage for this organism should be given when smear of the ulcer base suggests its presence. A topical ointment containing polymyxin in addition to subconjunctival and systemic gentamicin should be used.

This brings us to the three ocular inflammations which are most likely to require the combined efforts of the internist and ophthalmologist in both diagnosis and management.

Orbital Cellulitis

This disease is a severe, potentially lethal infection which may be accompanied by septic shock or cavernous sinus thrombosis, or both. The process is usually secondary to sinusitis, trauma, conjunctivitis, dacrocystitis or hemotogenous seeding from a remote source. Obviously, aggressive efforts should be extended to locate a primary source for the infection. Orbital cellulitis must also be differentiated from numerous other entities which may resemble an acute infection such as tuberculosis, syphilis, anthrax, sarcoidosis, Wegener's granulomatosis, phycomycosis, aspergillosis, lethal midline granuloma, xanthoma and inflammatory pseudotumor of the orbit.[45]

The most common organisms causing bacterial orbital cellulitis are S. aureus, S. pneumoniae, S. viridans and hemolytic streptococci.[42] However, Gram-negative rods, including Pseudomonas, have also been implicated. With the rising incidence of penicillin-resistant staphylococci an antibiotic, such as methicillin or cephalothin, in combination with gentamicin should be used for initial coverage. The complications of orbital cellulitis include cavernous sinus thrombosis, meningitis, dacrosystitis, severe lid scarring and panophthalmitis. If the initial antibiotic treatment is ineffective, the most fluctuant area of involve-

ment must be drained. Bacterial diagnosis should be attempted with needle aspiration of the involved area and Gram stain and culture. The advancing margin of the inflammatory area should be aspirated. Addition of warm compresses to the area of involvement may be beneficial.

Mucormycosis (Phycomycosis)

This infection almost always occurs in a setting of severe debilitation or diabetes. When associated with diabetes, ketoacidosis is usually present. The disease generally presents as a unilateral orbital infection associated with ophthalmoplegia and proptosis. It can result from either hematogenous spread or direct extension from the nasal sinuses. A black crusting material may accompany the exudate either around the eye or exuding from the nares. The specific diagnosis can usually be made by scraping the lesion and identifying the broad based nonseptate hyphae by direct microscopic examination. If material cannot be obtained directly from the eye, a swab of the nose should be examined.

The complications of this disease are devastating and the fatality rate approaches 90 percent. The most important complication is cavernous sinus thrombosis with subsequent intracerebral infection. The treatment of choice is systemic amphotericin B. Any patient presenting with orbital mucormycosis should have careful evaluation for the presence of infection elsewhere, particularly in the central nervous system, lung and gastrointestinal tract.[46] Further characterization of this infection is presented elsewhere in the symposium (see Part I).

Endophthalmitis

Generally, endophthalmitis occurs following surgical operation on the eye. Therefore, an ophthalmologist is usually the primary physician making the diagnosis in this situation. However, another important cause of endophthalmitis is hematogenous seeding of the eye and frequently a nonophthalmologist is the first physician to suspect this diagnosis. Hematogenous endophthalmitis may be a complication of infective endocarditis as exemplified by recent reports of endophthalmitis associated with staphylococcal endocarditis.[47] S. aureus is the most common cause of endophthalmitis with P. aeruginosa second. Because of the presence of the two organisms, use of an antistaphylococcal agent, such as methicillin, plus gentamicin should be used systemically for initial coverage. If a patient is allergic to penicillin then cephalothin or vancomycin may be substituted. In addition to the systemic route, the gentamicin should be given topically or subconjunctivally.

Recently a number of reports have emphasized the importance of fungal and fungal-like agents causing endophthalmitis. Probably the most common of these organisms is Candida.[48,49] These organisms not only can cause destructive ocular disease but also may be important clues to underlying disseminated mycosis. This type of endophthlamitis is best treated with systemic amphotericin B. 5-Fluorocytosine, either alone or in combination with amphotericin B, may prove to be an important agent as further clinical experience is accumulated.

These six eye diseases represent infectious emergencies and may result in permanent loss of vision and even death. Avoidance of these complications depends upon early diagnosis and early institution of appropriate therapy. Because of the high incidence of staphylococcal infection in the eyes and the potential for rapid ocular tissue destruction with Gram-negative rods, which are occasionally encountered, broad spectrum antibiotics should include agents effective against penicillinase-producing staphylococci and Gram-negative rods, primarily Pseudomonas. The toxicity of these antibiotics must be monitored carefully when given systemically.

TRADE AND GENERIC NAMES OF DRUGS

Penicillin G	*penicillin G*
Chloromycetin®	*chloramphenical*
Keflin®	*cephalothin*
Cleocin®	*clindamycin*
Garamycin®	*gentamicin*
INH®, Triniod®, Nydazid®	*isoniazid*
Myambutol®	*ethambutol*
Polycillin®, Omnipen®, Tocacillin®, Amcil®, Penbritin®, Principen®	*ampicillin*
Unipen®	*nafcillin*
Staphcillin®	*methicillin sodium*
Sulfonamide	*sulfonamide*
Anchromycin®, Panmycin®, Tetracyn®	*tetracycline HCl*
Mycifradin sulfate®	*neomycin*
Polymyxin B sulfate®	*polymyxin B sulfate*
Fungizone®	*amphotericin B*
Prostaphlin®	*oxacillin*
Vancocin®	*vancomycin*
Ancobon®	*5-fluorocytosine*
Keflex®	*cephalexin monohydrate*
Loridine®	*cephaloridine*
Dynapen® Pathocil® Veracillin®	*dicloxacillin*
Lincocin®	*lincomycin hydrochloride monohydrate*

Coly-Mycin S® ..... *colistin sulfate*
E-Mycin®, Erythrocin®, Kesso-Mycin®, Ilotycin®, Robimycin®, Pediamycin® ..... *erythromycin*
Kantrex® ..... *kanamycin*
Cyclamycin®, Tao® ..... *oleandomycin*
Albamycin® ..... *novobiocin*
Ristocetin ..... *ristocetin*
Streptomycin ..... *streptomycin*

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Refer to: The significance and treatment of long-term ventricular arrhythmias—Medical Staff Conference, University of California. West J Med 126:209-214, Mar 1977

Medical Staff Conference

The Significance and Treatment of Long-Term Ventricular Arrhythmias

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Associate Professor of Medicine, and H. David Watts, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, CA 94143.

DR. GOLDMAN:* This presentation will concern ventricular ectopy as it relates to the prognosis and management of patients with chronic heart disease. Supraventricular arrhythmias will not be discussed and ventricular ectopy in association with acute myocardial infarction will not be emphasized. This will not be a debate between the pros and cons of therapy. Neither Dr. Ryan nor I is convinced of the effectiveness of available drugs, but we cannot be oblivious to the problem. I will discuss the magnitude and severity of the problem and Dr. Ryan will present the results of current therapy.

I will begin with a brief review of electrophysiology. All arrhythmias can be explained as resulting from (1) alterations in automaticity, (2) conduction disturbances and (3) a combination of both. A ventricular muscle cell has a membrane resting potential (MRP) of −90 mV which is the result of the potassium gradient across the cell membrane. When the MRP is lowered to threshold potential (approximately −60 mV) there is a rapid influx of sodium ions (the fast current) resulting in depolarization (phase 0) (Figure 1). This is followed by a slow wave of repolarization divided into phases 1, 2 and 3. Calcium ions enter the cell during phase 2. Even during situations in which sodium influx is inhibited and phase 0 depolarization cannot occur, this calcium influx (the slow current)) can depolarize the cell. This is especially influenced by catecholamines. Cells of the His-Purkinje system have the property of diastolic depolarization due to intracellular retention of potassium. Under normal circumstances this is insufficient to reach threshold potential. However, as a result of many pathologic and physiologic circumstances, such as ischemia, injury, catecholamine excess, fever, hypoxia, hypercapnea, stretch, electrolyte abnormality or drug effect, this slope of phase 4 diastolic depolarization will be increased and reach threshold resulting in automatic discharge.

A reduction in MRP will lead to a reduction in the height and rate of rise of phase 0 depolarization. If this progresses over a series of cells, it will result in decremental conduction block. This block is undirectional. It prevents antegrade conduction but permits retrograde conduction and thereby initiates reentry, resulting in single or repetitive ectopic discharge.

*Mervin J. Goldman, MD, Professor of Medicine and staff member of the Veterans Administration Hospital, San Francisco.

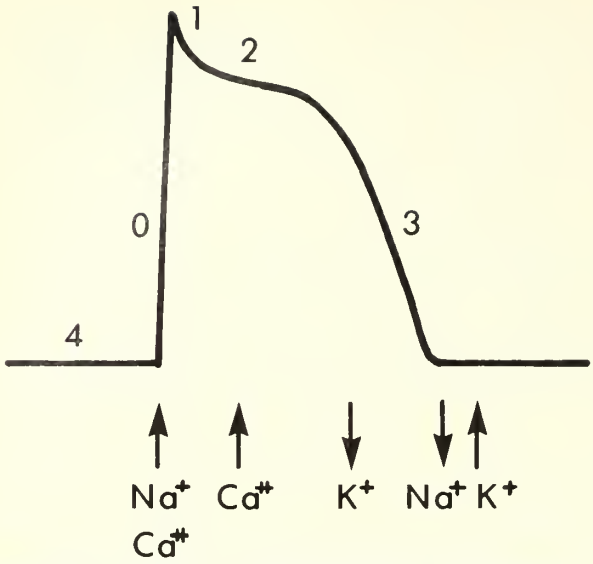

Figure 1.—Diagram of action potential of a ventricular muscle cell:

Phase 4: Membrane resting potential = −90 mV
Phase 0: Rapid depolarization due to Na^+ and Ca^{++} influx
Phase 1: Initial phase of repolarization
Phase 2: Plateau phase of repolarization in which there is a slow influx of Ca^{++}
Phase 3: Efflux of K^+ resulting in slow return of intracellular potential to −90 mV. At the termination of phase 3 the active transport system extrudes Na^+ from the cell and pumps K^+ into the cell.

Differences in refractory periods between adjacent areas of myocardium result in electrical instability. If the entire myocardium is uniformly hypoxic there will be no differences of electrical potential and no ectopic discharge. A localized area of ischemic myocardium will have a different duration of action potential than adjacent normal myocardium. Thus a difference of electrical potential will exist between these two zones and can result in ectopic discharge.

Although appreciating the electrophysiologic mechanisms by which ventricular ectopy is initiated, it is impossible for clinicians to determine which specific mechanism is responsible in any patient and accordingly "tailor" the therapy to be used. The importance of ventricular ectopy cannot be denied. Most, if not all, instances of sudden death are due to ventricular fibrillation. It is essential to attempt to identify those patients at high risk and try to offer therapy to prevent this complication.[1] The remainder of this discussion will center on ventricular ectopic beats as a predictive factor. The Lown classification of ventricular ectopy will be used[2] (see Table 1).

ABBREVIATIONS USED IN TEXT
ECG = electrocardiogram
MRP = membrane resting potential
PVC = premature ventricular contractions

Before one can attempt to evaluate the significance of ventricular ectopy one must have a knowledge of its prevalence in the general population. Three factors are of major significance: (1) age, (2) presence of cardiovascular disease and (3) duration of electrocardiogram (ECG) monitoring.

A study by Hinkle and co-workers[3] indicates the increasing incidence of ventricular ectopy with age. Six hour monitoring was done on a group of asymptomatic persons. The incidence of premature ventricular contractions (PVC) was as follows: 35 to 40 years old, 19 percent; 55 to 60 years old, 62 percent; 60 to 65 years old, 80 percent. These were mainly grade I and II ectopics, as defined by Lown.

Lown and co-workers[2] evaluated the frequency and severity of PVC's during 24-hour monitoring of 184 outpatients with known coronary artery disease. No ectopic beats were recorded in 12 percent, grade I in 17 percent, grade II in 6 percent, grade III in 25 percent, grade IVa in 27 percent, grade IVb in 14 percent. Of these 184 patients, cardiac arrests occurred in 13 outside of the hospital. No PVC's had been detected during monitoring in two patients, grade IV ectopy in ten and grade V ectopy in one. The grade V ectopy, that is, the R on T phenomenon, has been considered an ominous sign for predicting future serious ventricular tachyarrhythmias.[4] One report from a coronary care unit, on the contrary, concluded that these early PVC's were no more predictive of ventricular tachycardia or fibrillation than were late PVC's.[5]

The evaluation of the frequency and type of PVC's will depend on the duration of ECG monitoring. In one study of a group of patients with known

TABLE 1.—*Lown Grading System*[2]

Grade	
0	No PVC's
I	Occasional, isolated PVC's
II	Frequent (>1 per minute or 30 per hour)
III	Multiform PVC's
IV	Repetitive PVC's
	a. Couplets
	b. Salvos (three or more)
V	Early PVC (R on T phenomenon)

PVC = premature ventricular contractions

coronary disease, 10 percent were found to have PVC's by finding on routine ECG's.[2] It must be appreciated that such a recording involves less than one minute. In fact, most routine ECG's are only of 15 seconds duration. In the same patients, a three-minute record showed a 15 percent incidence of PVC's, and a 12-hour record 60 percent and a 24-hour record 85 to 90 percent PVC's.

Continued or intermittent electrical instability as shown by PVC's and sudden death has a number of characteristics. It is often more common in patients with angina, with or without previous infarction, than in those in whom myocardial infarction has occurred but who remain asymptomatic. The one-year mortality, including sudden death, is higher in a group of patients in whom subendocardial infarction is diagnosed than in those with a diagnosis of transmural infarction. A follow-up study of 234 patients discharged home after successful resuscitation from ventricular fibrillation indicated a 14 percent mortality in two years in those patients diagnosed as having had an acute myocardial infarction in association with the episode of ventricular fibrillation. This was in contrast to a 47 percent mortality in two years in those patients in whom myocardial infarction had not occurred.[6] I believe that patients with healed infarcts who have good ventricular function and are free of angina have a better prognosis because the zone of infarction and the remaining well perfused myocardium do not result in electrical instability and ventricular ectopy. Patients with angina or subendocardial infarction and survivors of ventricular fibrillation without infarction have more electrical instability manifested by PVC's with the ever present risk of sudden death.

Stress ECG's frequently show more ventricular ectopy than shown by routine ECG's in patients with coronary disease.[7] Lown's data indicate that more information is attained by 24-hour monitoring than by a single stress test.[2]

The severity of the coronary artery disease correlates with prognosis and the risk of sudden death. Approximately 97 percent of the sudden deaths in the study group reported by Margolis and associates occurred in patients with either triple vessel disease, poor left ventricular function or low cardiac output.[8] However, 74 percent of the patients with the same severity of disease were alive during the two-year period of observation. Ventricular ectopy had been previously detected in 21 percent of patients who died suddenly whereas 5 percent of survivors with heart disease of similar severity were known to have PVC's. The evidence supports the significance of ventricular ectopy as an independent predictor of sudden death. The Coronary Drug Project Research Group[9] reported on the follow-up of 2,035 survivors of myocardial infarction. Based on routine ECG records, the mortality was twice as great in those with known ventricular ectopy. Hinkle reports on the results of six-hour monitoring in a group of 300 working people whose average age was 55.[10] If PVC's were present with a frequency of more than ten per 1,000 beats, subsequent mortality was increased ten fold. Kotler and co-workers have reported on the prognostic significance of ventricular etopic beats with respect to sudden death in the late postinfarction period.[11] A total of 160 ambulatory survivors of myocardial infarction, all under age 65, were studied over periods of 12-hour monitoring during 30 to 45 months. There was a 13.8 percent incidence of sudden death (within one hour) in those with frequent or advanced grades of ventricular ectopy as opposed to a 3 percent incidence of sudden deaths in those who had not evidenced PVC's.

The role of the sympathetic nervous system in the genesis of ventricular ectopy is worthy of comment. It is of interest to review data on patients with heart transplants at Stanford. Even though in these patients there have been acute myocardial infarctions and rejection phenomena, ventricular ectopy is a rare occurrence. In patients with a form of congenital heart disease characterized by a long QT interval, ventricular arrhythmias and sudden death, improvement has been reported after left stellate ganglionectomy. Whether this approach to treatment may have a role in patients with coronary disease is unknown.

So far I have emphasized the significance of ventricular ectopy in patients with coronary disease. A similar situation exists in association with hypertensive heart disease. The Framingham study and other studies have shown to two- to three-fold increase in mortality in patients with left ventricular hypertrophy when ventricular ectopy is present as an independent variable. In patients with idiopathic cardiomyopathy the increased morbidity and mortality due to associated arrhythmias is well known.

Dr. Ryan will discuss in depth the currently available drugs that are used, but first I will briefly review them: (1) Lidocaine is very effective and relatively nontoxic but limited by its

requirement for parenteral administration. Oral analogues are being evaluated and seem promising. (2) Quinidine and procainamide are known to reduce the incidence of ventricular ectopy and raise the threshold for ventricular fibrillation in animal experiments. These drugs act by (a) reducing phase 4 prepotential thereby reducing automaticity and (b) prolonging conduction. This latter effect can prevent reentry but also can produce ventricular ectopy. (3) Propranolol, in addition to its beta adrenergic blocking action, has a "quinidine-like" action. This is documented by analogues of this drug which are devoid of beta blockade. (4) Diphenylhydantoin has not been shown to be of clinical value with the exception of the treatment of digitalis induced arrhythmias. (5) Digitalis is of value in reducing or eliminating ventricular ectopy in patients with congestive heart failure. There are clinical experiences suggesting that digitalis is of benefit in the absence of failure. This requires further investigation. (6) Bretylium has antiarrhythmic properties but its effect is limited by its hypotensive action. Newer derivates of this drug are being investigated. (7) Verapamil is an investigational drug in this country (though it is available in Europe). One of its modes of action is the inhibition of the slow current calcium influx. The long-term effectiveness of any of the above drugs in the management and control of chronic ventricular ectopy remains to be proven.

In conclusion, there is no question that sudden death due to ventricular fibrillation is of major importance in patients with coronary and hypertensive heart disease. Animal studies and clinical experiences in coronary care units have established the value of control of life threatening ventricular ectopy. The presence of PVC's and especially the more serious grades of ventricular ectopy have predictive value, independent of other variables. Even if the ventricular ectopy cannot be eliminated, it is theoretically possible that drug therapy can reduce the incidence of ventricular fibrillation by raising the threshold of this arrhythmia.

All that remains is to have available drugs that are effective, relatively nontoxic and not arrhythmogenic in themselves. Dr. Ryan will now continue this discussion.

DR. RYAN:* Dr. Goldman has very eloquently outlined the problem and some of our approaches to the treatment of chronic ventricular arrhythmias. It falls to me to examine the efficiency, safety and usefulness of our modes of therapy. While there are nearly 300,000 sudden deaths from coronary disease in this country each year,[12] many of these are completely unpredictable. Stamler has indicated that 20 percent of all deaths in patients free of evidence of coronary heart disease are sudden.[13] In the Framingham study the first manifestation of coronary disease was sudden death in 11 percent of men.[14] Obviously these patients cannot be readily identified. But let us look at the literature and our own experience with the patients at risk as outlined by Dr. Goldman.

Our first approach to ventricular arrhythmias should be to avoid causing them. In a large proportion of patients in a general hospital in whom cardiopulmonary arrest occurred, an iatrogenic cause was not infrequently suspected.[15] Caution in the use of intravenously given medications such as aminophyllne, atropine, furosemide and lidocaine is warranted. Obviously underlying hypoxia and electrolyte disturbances should receive prime attention. Withdrawal of noxious stimuli such as caffeine, alcohol, cigarettes and amphetamines may have a major bearing on the control of ventricular as well as supraventricular arrhythmias.

Identification of the type of arrhythmia is also important. While accelerated idioventricular rhythm and ventricular parasystole are thought by some to be benign requiring no treatment at once, the long-term prognosis of these rhythms is not certain and even changes in treatment of these rhythms in acute situations is now under some debate. There may be further difficulty in distinguishing aberrancy from ventricular ectopy. Without a His bundle electrogram this may be impossible. Ventricular arrhythmias associated with mitral regurgitation may also have a different prognosis than when associated with ischemic disease, but may not be benign.[16]

Modes of therapy for ventricular arrhythmias are outlined in Table 2. The remainder of the dis-

TABLE 2.—*Modes of Therapy*

A	Correction of underlying abnormalities—pH, electrolytes, hypoxia, etc.
B	Withdrawal of noxious stimuli—drugs, alcohol, cigarettes, coffee, etc.
C	Specific drug therapy with antiarrhythmic agents
D	Pacing—overdrive suppression
E	Surgical operation—aneurysmectomy, coronary bypass, sympathectomy, and Stellate ganglionectomy

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cussion will be devoted to the more direct interventions—antiarrhythmic drugs, overdrive suppression and cardiac surgical procedures. Drugs available for chronic suppression of arrhythmias in this country are quinidine, procainamide, propranolol, diphenylhydantoin and digitalis. Table 3 indicates the results of the more recent trials carried out on alprenolol, practolol, pronestyl and diphenylhydantoin as agents to prevent sudden death. Only practolol and procainamide contributed significantly to the reduction of sudden death. Practolol is no longer available due to its serious side effects.[17] Procainamide is also unsuitable for long-term use because of adverse reactions.[18] Neither alprenolol[19] nor diphenylhydantoin[20] has proved to be of any value.

Studies on the effects of drugs on the frequency of ventricular arrhythmias are more abundant, but are no more encouraging (Table 4). No beneficial effects on arrhythmias were found with use of diphenylhydantoin, propranolol and quinidine.[21] In another study a reduction of arrhythmias occurred with procainamide but chronic use of this drug is hazardous.[22] Diphenylhydantoin did not reduce recurrence of ventricular tachycardia.[23] In only four of 16 patients was there a reduction in PVC's with quinidine or pronestyl.[24] Winkle and associates indicated the great difficulty of treating symptomatic patients with ventricular arrhythmias.[25] In most patients in his group there were frequent arrhythmias even after surgical operation or the use of combinations of potent drugs.

Even if our drugs were without side effects and our patients were 100 percent compliant, reduction in sudden death or even significant reduction in arrhythmias cannot be accomplished with drugs in most patients. Currently available drugs are hazardous. The same arrhythmias which we try to suppress may be produced by the drugs we use.[26] The mortality of ventricular arrhythmias associated with digitalis toxicity is still high. Lown advocates the use of digitalis in some patients with chronic PVC's even in the absence of ventricular dysfunction.

While the drugs available at present do not provide adequate control of arrhythmias or prevention of sudden death, newer drugs show more promise. The orally administered lidocaine derivatives and more specific beta adrenergic blockers may provide effectiveness without drastic side effects. Overdrive suppression has not met with great success in our experience, but this form of treatment may be useful on occasion when combined with medications. The logic of increasing heart rate to suppress arrthythmias in a patient who may have ischemia as a basis for his instability appears to be the breakup of reentry pathways by conduction through alternate Purkinje systems.[27]

Use of coronary artery bypass alone for control of arrhythmias is seldom successful except in the "Prinzmetal syndrome." In our experience there has been a pronounced reduction in sudden death in 200 patients following coronary artery bypass operations. In a follow-up period of 22 months after operation, only one patient has died suddenly.[28] Aneurysmectomy or infarctectomy with or without coronary bypass is far more successful.[25] Epicardial mapping is an embellishment which allows identification of reentry pathways.[29]

TABLE 3.—*Effects of Antiarrhythmic Agents on Sudden Death*

Author	*Drug*	*Drug Mortality*		*Placebo Mortality*		*Duration of Study*
		No. Patients	*Percent Dying*	*No. Patients*	*Percent Dying*	
Reynolds[20]	Alprenolol	39	9	38	9	1 year
Kosowsky[18]	Procainamide	39	3	39	15	2 years
Collaborative Group[19]	Diphenylhydantoin	285	10	283	10	1 year
Multicenter International Study[17]	Practolol	1,524	3	1,514	4	1 year+

TABLE 4.—*Effects of Antiarrhythmic Drugs on Frequency of Arrhythmias*

Author	*Drug*	*No. Patients*	*Effects on No. PVC's*
Kennedy[21]	Diphenylhydantoin	8	None
	Propranolol	8	None
	Quinidine	9	None
Gey[22]	Procainamide	23	105±108 vs 38±69
Stone[23]	Diphenylhydantoin	10	None
Jelinek[24]	Quinidine	16	Decreased in 4 patients
	Procainamide	16	Decreased in 4 patients

Surgical sympathectomy has short-term effects on arrhythmias and often will not reduce the frequency.[30]

Stellate ganglion blockade has been shown successful in reducing arrhythmias in a small number of cases,[31] but these patients did not have ischemic heart disease. In one of our own cases left stellate block using bupivacaine hydrochloride produced prolonged sympathetic block, but had no discernible effect on the frequency of arrhythmias. This remains to be tested as a mode of therapy for chronic ischemic arrhythmias.

What then can we do about chronic ventricular arrhythmias and the high incidence of sudden death which they may produce? We can do very little. Perhaps a major thrust in preventive medicine is required. Education of the American people to understand the hazards of smoking, hypertension, obesity and lack of exercise might reduce the problem to manageable proportions. Continued effort must be maintained to identify those patients who are at special risk. More specific drugs with fewer and less serious side effects are needed to replace the dangerous and relatively ineffective agents now available to us. The problem of recurrent ventricular arrhythmias is a serious one. It merits the attention of cardiologists, surgeons and pharmacologists if adequate therapy is to be developed.

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Important Advances in Clinical Medicine

Epitomes of Progress—Radiology

The Scientific Board of the California Medical Association presents the following inventory of items of progress in radiology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in radiology which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Radiology of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, California Medical Association, 731 Market St., San Francisco, CA 94103

Cholecystokinetic Cholecystography

THE NORMAL physiologic mechanism resulting in gallbladder contraction is set in motion by food ingestion which initiates neural and hormonal stimuli that stimulate the biliary system. Cholecystokinin is released from the duodenal mucosa in response to the presence of fat and lipolytic products in the small intestine, and to a lesser degree by amino acids and small peptides. It stimulates contraction of the gallbladder and simultaneous relaxation of the sphincter of Oddi, inhibits gastric emptying and increases intestinal motility. Cholecystokinin is a 33 amino-acid polypeptide. However, the C-terminal octapeptide fragment (sincalide) reproduces all the known biologic activities of the entire intact molecule. A study of 40 patients in whom oral cholecystography was required as part of the clinical evaluation showed that the intravenous administration of the C-terminal octapeptide fragment of cholecystokinin, sincalide, affords a safe and effective agent for gallbladder contraction with resultant excellent cystic and common bile duct visualization. Maximum contraction of the gallbladder (40 percent or greater reduction in size) occurs within 5 to 15 minutes after injection of sincalide. Peak gallbladder contraction occurs earlier than that after a fatty meal. The only significant side effects of the procedure are mild nausea and occasional vomiting. Intravenously given sincalide circumvents the problem of unpredictability of response of the gallbladder to a fatty meal and variability in the rate of release of endogenous cholecystokinin.

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Ultrasound in the Evaluation of Abdominal Aortic Aneurysms

ULTRASOUND IS PRESENTLY the diagnostic procedure of choice in the evaluation of pulsatile abdominal masses. It is simple, noninvasive and more accurate than physical examination, plain roentgenography, aortography or isotope aortography in the diagnosis of abdominal aortic aneurysms. Aortography may miss or underestimate the size of a noncalcified aneurysm containing thrombus, while ultrasound will show accurately overall aneurysm size, presence and location of intraluminal clot, and caliber of actual lumen. In addition, ultrasonography is capable of distinguishing paraaortic abdominal masses, such as pseudocysts of the pancreas, which may be indistinguishable clinically from an aneurysm.

Once the definitive diagnosis of an abdominal aortic aneurysm has been established by ultrasonography and a decision to operate has been made, routine preoperative aortography is not always necessary despite the fact that ultrasound usually is not able to show the relationship of the aneurysm to the renal arteries nor pathological involvement of the branch vessels of the aorta. Use of further preoperative workup, including arteriography, should be reserved for those patients with suspected renal artery stenosis or ischemia of the mesenteric circulation or of the lower extremities.

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Tuberculosis of Bone and Joint

TUBERCULOUS OSTEOMYELITIS and tuberculous arthritis often go unrecognized by physicians. A misleading clinical hystory as well as a "nonclassical" radiographic picture contribute to the delay in diagnosis. Frequently, the patient relates the onset of musculoskeletal pain to a specific episode of trauma, thus misleading the clinician as to the chronicity of the problem.

Because of the indolent nature of tuberculous infections, the joint may appear normal or, at most, a distended joint capsule from fluid and synovial hypertrophy may be seen. Occasionally, marginal erosions of the articular surfaces of bone and narrowing of the joint space are noted on the initial examination. Tuberculous osteomyelitis classically appears as a well-circumscribed lytic lesion, but a more aggressive form of the organism causes a permeative destructive pattern with periosteal reaction, identical to a pyogenic infection.

A review of the literature shows that in 75 percent of patients with skeletal tuberculosis there are pulmonary changes. In our experience, no abnormalities are seen on most x-ray films of the chest in these patients. Therefore negative findings on an x-ray film of the chest should not dissuade one from the diagnosis of tuberculosis.

In most cases of skeletal tuberculosis, the skin test is positive. Therefore a negative skin test would argue against the diagnosis of tuberculosis. To avoid delay in diagnosis, in any case of monoarticular arthritis or in an aggressive monostotic bone lesion aspiration or biopsy must be done and the specimen sent for acid fast bacteria culture, despite a misleading history or radiographic appearance.

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Ultrasonography of the Biliary System

IN RECENT YEARS ultrasound tomographic images have significantly improved. This improvement, termed gray scale, makes it possible to show abnormal morphologic changes in the biliary system more accurately. The general advantages and disadvantages of ultrasonography have been widely publicized. Specific advantages of this method for biliary tract imaging are that ultrasonograms require no contrast agents and that image quality is independent of hepatic or biliary function.

The gallbladder can be visualized in approximately 95 percent of fasting persons. Gallstones are recognized by high amplitude acoustical reflections within the gallbladder. Additionally, most stones so strongly attenuate the sound beam that an "acoustic shadow" is produced. Decubitus or erect views are used to show that stones gravitate to dependent positions.

Not all gallstones produce strong reflections or "acoustic shadows." A paucity of bile within the gallbladder or a severely contracted gallbladder complicates the ultrasonographic diagnosis.

Normal sized intrahepatic bile ducts are not visible on ultrasonograms. Occasionally normal sized extrahepatic bile duct components can be shown to be present. Conversely, it is possible to show dilated intrahepatic and extrahepatic bile ducts. Therefore, ultrasonography is highly valuable in jaundiced patients in whom noninvasive radiographic contrast examinations may be impossible. The ultrasonographic findings aid in the selection of patients in whom additional invasive diagnostic procedures may be needed, such as endoscopic retrograde cholangiopancreatography or percutaneous cholangiography. In addition, a mass such as carcinoma of the pancreatic head or gallstones may be shown to be the cause of the obstruction.

The major indications for ultrasonography of the biliary system are: (1) jaundiced patients in whom studies using orally or intravenously given contrast material are precluded, (2) patients in

whom it is not possible to study the gallbladder radiographically but in whom it is desired to show the presence of stones, (3) patients who are allergic to radiographic contrast agents, (4) patients in whom findings on an oral cholecystogram are suspicious but not diagnostic for stones, (5) pregnant patients with jaundice or suspected cholelithiasis and (6) patients in whom the emergency nature of the clinical problem precludes the delays inherent in studies using orally given contrast agents and frequently involved in examinations using intravenously administered contrast agents.

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Bone Scanning in the Staging of Breast Cancer

THE THERAPEUTIC APPROACH to breast cancer remains an unresolved and controversial problem. Presently, the rationale for radical surgical procedures is based on the premise that the tumor has not spread beyond the breast and regional lymph nodes. For this reason it is important to evaluate the patient for metastatic disease before definitive surgical operation.

The value of preoperative bone scanning in detecting distant spread was emphasized in a study in which 47 patients with breast cancer (stage I or II) were examined with bone scans within three months of clinical presentation. In 19 (40 percent) of these 47 patients there were abnormal findings on bone scans consistent with metastasis, and in 16 of these 19 patients metastasis from breast cancer was confirmed by biopsy results. These data, obtained from postoperative patients, document the presence of early metastasis to bone in breast cancer, and underscore the need for routine preoperative bone scanning.

The sensitivity of radionuclide bone scanning in screening patients with breast cancer for bony spread has been shown to be superior to routine radiographic survey, serum alkaline phosphatase determination or identifying the presence of bone pain. In ten of 31 patients with breast cancer who were examined with both scans and conventional x-ray bone surveys, the scan detected lesions indicating possible metastatic disease in sites associated with normal findings on radiographs; in only one patient did the scan give negative findings when the radiograph gave positive ones. Another study compared the sensitivity of bone pain as an indicator of metastatic disease with the results of the bone scans. In 20 patients with breast cancer positive findings on bone scans indicated possible metastatic disease in the absence of bone pain. The same study also compared alkaline phosphatase determinations and bone scans in 76 patients with breast cancer; in 29 (38 percent) there were positive scans associated with normal alkaline phosphatase values. These results appear to indicate that bone pain and an elevated serum alkaline phosphatase value, the traditional indicators of early metastatic spread, are not as sensitive as bone scanning in detecting the early spread of breast cancer to bone.

In a Scottish study, preoperative bone scans were done in 78 patients with breast cancer in whom no evidence of metastatic disease was seen on bone radiographs. Results of bone scans were abnormal in 35 patients; the abnormal findings on scans in 12 were associated with benign processes. The remaining 23 patients in whom findings on scans suggested metastatic disease are being followed and in 10 clinically apparent metastasis has already developed.

The previous studies have shown that a significant number of patients with breast cancer will have bony metastasis which can be detected by bone scanning even though the patient is asymptomatic and the serum alkaline phosphatase values and radiographic findings are normal. Based on this evidence, the following sequence is suggested, especially when radical surgical operation is contemplated:

- Total body bone scan.
- Radiographs only of regions which appear abnormal on bone scan or which are clinically symptomatic.
- Biopsy (when feasible) of scan-positive and radiographically negative regions.

This procedure should identify a population of women with metastatic disease and thereby spare them the risk, disfigurement and discomfort of unnecessary radical surgical procedures.

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Oat Cell Carcinoma of the Lung: Modern Radiotherapeutic Management

DESPITE THE RESPONSIVENESS of oat cell carcinoma of the lung to both radiation therapy and chemotherapy, the five-year survival rate remains dismally and paradoxically low. Yet, just as the early improvements noted in the treatment of childhood leukemia were small but encouraging, there is considerable reason for optimism with intensive treatment of a combined modality approach.

There is little doubt that oat cell carcinoma is a systemic disease at presentation. In almost half of the patients bone marrow involvement will be noted at the time of diagnosis. Disseminated disease is found at postmortem examination in virtually all patients.

Findings in two recent studies using a combined modality approach have shown definite improvement in survival rates. In each study, treatment was begun with cycles of multiagent chemotherapy including the use of cytoxan. After a patient responded to treatment, a two-week course in radiation therapy to the mediastinum was then sandwiched between cycles of chemotherapy. Both studies reported median survival times of about nine months with several patients alive after 18 months. Although not dramatic, it is the first encouraging development in the results of treatment for patients with oat cell carcinoma of the lung.

As in childhood leukemia, a prolongation of survival of these patients has led to the recognition of a high probability (about 40 percent) of symptomatic brain metastasis occurring despite chemotherapy. Presumably, chemotherapeutic agents which are effective throughout most of the body are not able to cross the blood brain barrier in doses adequate to control microscopic tumor. Therefore, patients who respond to chemotherapy would probably benefit by undergoing a course of radiation to the brain, even when overt central nervous system involvement has not been proved. The well-recognized radiosensitivity of oat cell carcinoma suggests that cranial radiation can be both effective and safe in modest doses of about 3,000 rads over two weeks.

Integrated treatment consisting of systemic multiagent chemotherapy and localized radiotherapy to the primary lesion and the brain may prove effective in reducing systemic relapses as well as prolonging the length of survival. It is hoped that such an integration of radiation therapy and chemotherapy will prove to be an optimal model for the management of other human neoplasms.

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Small Bowel Examination by Duodenal Tube

REPORTS OF small bowel examination by duodenal intubation extend back to the early 1920's, and since that time there have been scattered successful reports using this technique. Despite success, small bowel examination by duodenal intubation only recently has gained some acceptance in major radiological centers of Europe and Scandinavia. This method has been available for a number of years and should be used more often to evaluate small bowel disease.

Duodenal intubation yields more information because the small bowel is filled directly rather than by gastric emptying. A much larger bolus of contrast material reaches the small bowel which produces better filling and therefore a much better examination. The examination usually is done using a standard duodenal tube, the same tube which is used for hypotonic duodenography. As in hypotonic duodenography, a guidewire is sometimes used to direct the tube toward the gastric antrum to the gastric outlet. With the tip of the tube at the ligament of Trietz, the tube is connected to a container of barium and the examination is then begun under fluoroscopic control. A barium suspension with a specific gravity of 1.16 to 1.32 should be used for ideal results. Spot films are taken as the barium passes through the small bowel so that every portion of the small bowel has been recorded on film. A compression device is used to separate the distal ileum in the pelvis. When the barium suspension has reached the cecum, air or water can be instilled into the duodenal tube giving a double-contrast examination for better mucosal detail. An adequate small bowel examination by this technique usually requires only 15 to 30 minutes.

Small bowel examination by duodenal intubation should be considered whenever accurate small bowel information is necessary. It has been espe-

cially helpful in the diagnosis and management of patients with Crohn's disease. It is also useful in showing the presence of small bowel neoplasm like carcinoid and in showing there to be a Meckel's diverticulum.

The success of this technique is greatly dependent on the enthusiasm of the physician toward gastrointestinal radiology and his skill as a fluoroscopist. The routine use of this technique is a new approach for examining the small bowel and the results have been excellent in centers where it has been used. Although routine use of this technique may not be practical in the United States, use in selected patients will produce gratifying results and accurate diagnosis.

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Gray Scale Ultrasonographic Differentiation of Medical and Surgical Jaundice

THE RECENT technological advances in ultrasound instrumentation including gray scale signal processing and focused transducers have led to the improved visualization of many normal structures in the high retroperitoneum and liver. Most of the important upper abdominal vasculature, all or part of the glandular elements of the pancreas, and portions of the normal biliary system can be seen in a high percentage of patients using the newer scanning techniques and commercially available instrumentation. An immediate benefit from this improved resolution has been the accurate differentiation between surgical and medical jaundice. Although considerable experience is required to distinguish the dilated intrahepatic or extrahepatic biliary system from the upper abdominal vasculature, once learned, the differentiation between obstructive and nonobstructive jaundice can be made with greater than 95 percent accuracy. Rarely, extreme gassiness in the upper abdomen, an interposed right colon or residual barium will prevent the ultrasound examination from being diagnostic.

On the basis of these initial reports, a new diagnostic sequence has been adopted for jaundiced patients. If the degree of bilirubinemia precludes conventional oral or intravenous cholangiography, then gray scale ultrasound is the initial imaging procedure. If a normal or nondilated biliary system is shown by the ultrasound examination, then either clinical observation is instituted or a biopsy study of the liver done. When gray scale ultrasound examination shows a dilated biliary system, then the clinician has the option of either obtaining further specific diagnostic information by outlining the biliary tree with transhepatic or transjugular cholangiography or going directly to surgical exploration.

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EDITORIALS

Continuing Medical Education and Continuing Professional Competence

THESE ARE DAYS of public accountability for medicine. Among other things the public wants to be assured that every physician is competent and remains competent to do whatever he or she is supposed to be doing in patient care. And for a number of reasons continuing medical education is becoming tied to continuing professional competence. The logic in general appears to be that if education made a physician competent in the first place, then continuing education should make for continuing competence. In any case a number of professional societies now demand evidence of continuing education for continued membership and some state governments have established continuing education requirements for the reregistration of a physician's license. However, a direct relationship between any particular continuing education experience and a change in a physician's practice behavior or in practice outcomes has been difficult to demonstrate and the assumption that there is a relationship is actually being questioned. But on the other hand it is obvious enough that physicians do not practice with only the knowledge and skills they used 5, 10 or 20 years ago when they may have completed their initial training. Somehow new knowledge and skills have been acquired, and this by definition is continuing education.

In California a new law (which was supported by the California Medical Association) addresses the problem more specifically. It seeks to link continuing medical education with continuing competence, with physician performance in his or her own practice, and with mechanisms for quality review, and this again with continuing medical education—thus completing a kind of circle of linkages. This is precedent setting. So far there is very limited information and experience with just how these linkages can be established or with how what is or is not accomplished can be measured. But the goal seems to be a reasonable one for both profession and public, and it poses a fascinating educational challenge.

The problem quickly gets down to what is meant by professional competence and how one can determine whether it is or is not present. Competence is hard to define and harder to measure. It certainly is not fixed. Rather it changes with a practice situation or even with a practice problem. A physician may be competent to handle the problem one patient presents but not the problem of the next. A number of things quickly surface as possible or even probable components of physician competence. The most obvious is the need for current scientific or cognitive knowledge. A competent physician must also have up-to-date practice skills. These are of several kinds: technical skills as in surgical or other technical procedures, for example; managerial skills for cases where the services of a variety of health professionals are brought into play; problem-solving skills for both diagnosis and treatment, and communication skills for interacting with patients, their families and others who are properly involved in the care of a patient. And a competent physician should have attitudes of caring and concern and respect for the dignity, the rights and the personal values of the human being who is the patient. Performance and outcome are attributes of competence. It is also likely that a competent physician should not be wasteful of anyone's time or money. There should be cost effectiveness in administering the practice, and a favorable cost benefit for the diagnostic and treatment programs which are advised and carried out. And finally physician competence should produce satisfaction—satisfaction for the patient, for the physician and for society which now pays for so much of health care.

The objectives of continuing medical education to assure this continuing physician competence cannot yet be well defined because physician competence itself is not yet well defined. But it already seems obvious that its dimensions will need to be expanded considerably from what

has been traditional. Ideally, continuing medical education should have the capability to address all the components of competence as these may eventually be identified and defined. Ideally it should result in change in a physician's practice behavior when this is necessary or desirable, and to accomplish this it will be necessary for it to convince physicians that to change will really make a difference in the care or outcome for patients. Obviously if it will make little or no difference there is little or no reason to change—a point which is lost on some behavioral scientists who believe that behavioral change more or less automatically results from programmed information.

And finally, continuing education ideally should encompass more than simply educating a physician about those things commonly seen in his or her particular practice. A hallmark of a truly competent physician is having the knowledge to be aware of, recognize and know what to do about (or what can be done about) problems that are not frequently seen or are even rare. And then there are social and economic developments that increasingly affect patient's rights and patient care with which a competent physician must be familiar. All of this suggests that the objectives and content of continuing medical education will undergo considerable change, reinforcement and refinement as its art and science develop into an increasingly effective instrument to assure the continuing professional competence of physicians in practice. There are many changes ahead in this field and they should be changes for the better.

—MSMW

The Role of Testing in Coronary Artery Disease

EXERCISE stress testing has achieved wide acceptance as a simple, relative inexpensive, noninvasive means of evaluating the physiological consequences of coronary disease—myocardial ischemia. Its safety remains laudably unparalleled by all but the simplest procedures, the combined morbidity and mortality arising from this technique being estimated at under four per 10,000.[1] No test is without its imperfections, however, and it becomes essential for physicians employing any procedure to become fully conversant with its strengths, weaknesses and vagaries. Many of the problems in treadmill exercise testing are brought into focus in the paper by Abbott, Tedeschi and Cheitlin in the current issue of this journal, although it should be stressed in critique that the San Francisco General Hospital house staff does not necessarily reflect the practices of community physicians. The study serves as a valuable springboard for further discussion of exercise testing and its attendant difficulties.

The *sensitivity* of a test is defined as the percent of patients who have disease and in whom there is an abnormal test result. A substantial element of the treadmill test's insensitivity is now well established: in only approximately 65 percent of patients with anatomically significant coronary disease (luminal narrowing in excess of 50 percent of the vessel diameter) will there be a positive response.[2] A common misunderstanding, in the experience of Abbott and colleagues, centers around the fallacious belief that normal findings on a test serve to exclude the presence of coronary disease. Clearly, the 35 percent level of test insensitivity cited above attests to the erroneousness of this notion.

Causes of *false negative tests* include[2-4] (1) performance of inadequate levels of exercise (the concept of graded, maximal exercise has evolved over the years, based on the observation that a 10 to 20 percent increment in positive responders accrues when maximal or near-maximal degrees of activity are achieved); (2) presence of isolated single vessel disease, which is associated with normal test results in 55 to 60 percent of the instances (small areas of ischemia in the myocardium frequently remaining undetected electrocardiographically); (3) presence of coronary disease in the absence of ischemia (because an infarct has occurred distal to the obstructed vessel, because coronary lesions of between 50 and 75 percent may be insufficient to interfere with blood flow or because an area of ventricle is supplied by collateral vessels); (4) failure to monitor the proper lead(s) (utilizing either a unipolar or bipolar lead approximating V5 or V6, or several orthogonal leads, enhances the diagnostic yield by 5 to 15 percent), and finally, (5) simple test fallibility.

The other side of the coin is not covered in such great detail in the current paper: test *specificity* is also imperfect, albeit to a considerably

lesser degree. Specificity, defined as the percent of normal persons in whom test findings are negative, runs about 90 to 93 percent in most series,[2] so that one in 10 to 12 positive exercise electrocardiograms are, in effect, falsely positive responses, not reflecting coronary disease. Although it has been believed in the past that many of these cases represent ischemia due to nonatherosclerotic factors (intrinsic metabolic disease of the myocardium interfering with oxygen utilization, small vessel disease, hemoglobin-dissociation defects and the like have all been proposed as possible mechanisms), proof remains lacking in the vast majority of cases, and it is the belief of this writer that in most instances simple fluctuations of the ST segment induced by a variety of physiological or pharmacological phenomena misguide the interpreter into an incorrect diagnosis.*

Baseline depressions or abnormalities of the ST and T segments; hyperventilation-induced changes; mitral valve prolapse related to myxomatous degeneration within the leaflets; hypokalemia; use of a variety of drugs such as the digitalis glycosides, quinidine and the phenothiazines; left ventricular hypertrophy; the Wolff-Parkinson-White syndrome, and left bundle branch block each has the potential of contributing to a falsely positive test result.[8] Test nonspecificity, then, rises to an even higher percentage than that quoted above when one or more of these aforementioned features is present, and the interpretation of a stress electrocardiogram should be made with special caution under such conditions. We invariably analyze a supine and standing electrocardiogram and one taken after the patient hyperventilates for 1 to 2 minutes, and if the ST segments or T waves vary substantially during these maneuvers the test is considered uninterpretable, due to the enhanced likelihood of a false positive result. In the presence of *baseline abnormalities,* further depression of ST segment—especially when exceeding 2 mm in magnitude—is cited[5] as a valid index of ischemia, although in this writer's opinion the data supporting this hypothesis remain inadequately sparse. Finally, in this context, *frank misunderstanding by the interpreter* as to which changes constitute signs of ischemia stands out as a frequent cause of incorrectly diagnosed stress tests; all too frequently, the appearance of T wave inversions, ventricular arrhythmias, left bundle-branch block (LBBB), or simple 2 to 3 mm junctional depression with upward sloping ST segments are considered diagnostic of coronary disease, a position also unsubstantiated by available information.

The paper in the current issue also brings attention to the point that treadmill testing may be of benefit in selecting from the coronary population as a whole, those with severe degrees of coronary involvement. In recent studies from our laboratory[2,6] the value of this procedure in *quantifying* the severity of disease was presented in detail, and in that and other studies it was noted that pronounced depth of ST depression, depressed downsloping ST segments, early onset of ischemia and prolonged duration of ischemia each correlated with malignant or advanced types of coronary narrowing, such as main left and two and three vessel coronary involvement.

Finally, attention should be directed in this editorial, as it was in the paper by Abbott and his associates, to providing an understanding of the importance of the particular *population of patients* being considered for exercise testing. In those with definite or highly probable coronary disease, specific questions to be answered include: whether pronounced ischemia is present, and therefore whether coronary angiography or surgical operation should be considered; whether the patient has as yet unidentified exercise-induced ventricular arrhythmias; whether hypotension occurs during activity, and whether a particular level of exercise is reasonably well tolerated by the patient. Any or all of this information aids in managing or following a patient over a period of time and can be used, for example, in conjunction with drug therapy, titrating a patient's response to a particular dose of antianginal or antiarrhythmic medication. In addition, physical conditioning of patients with angina and those having had myocardial infarction or recent bypass graft surgical procedures is facilitated, and the safety of this type of rehabilitation program is thereby enhanced. In this particular subgroup of the coronary population test sensitivity, specificity and predictive accuracy—the likelihood that a positive test correctly recognizes the presence of ischemia—maintains an acceptably high level, and the procedure remains an invaluable adjunct in the management of such cases.[7] Moreover, a *prognostic value* is noted from early postinfarction exercise testing. DeBusk and colleagues found

*Coronary spasm in the absence of atherosclerotic coronary narrowing may produce ischemic pain; but insofar as we know today in the vast majority of cases this results in resting angina with ST segment *elevation*. The exercise response under these circumstances is usually normal.

that recurrent coronary events were heralded by the appearance of positive stress tests carried out 3 and 11 weeks following the infarction.[8]

In the population with atypical chest pain—that group where the physician becomes doubtful about the diagnosis of coronary disease—a negative test result, while not excluding coronary involvement with certainty, also serves as a reassuring collaborative point. It is of particular note in this regard that the long-term prognosis in patients with normal test results is from 5 to 14 times greater than in those with a positive finding on a stress test.[7,9]

The procedure probably falls to its nadir of usefulness in the routine *screening* of the adult, asymptomatic population, those having "executive" physical examination or those in whom "curiosity" as to the possibility of coronary disease exists. In this group, especially in cases where the patients are relatively young, the likelihood of coronary disease in any given case is sufficiently low that false positive responses are encountered more commonly (see articles by Froelicher[7] and Redwood[10] for details on this point). The examining physician, then, encounters the undesirable situation of having detected a positive test result in an asymptomatic person, with the dilemma of then having to decide to proceed with angiography, frightening the patient with the knowledge of a (possibly erroneous) positive test result, curtailing the patient's activity or obscuring the information. All too often in such instances, the patient is led down the primrose path of angiography and possible bypass surgical operation, in many cases, it is suspected, where anatomical coronary narrowing in the absence of ischemia was actually present. The problems encountered in dealing with *any test* in a population having a low disease prevalence is not unique to treadmill testing, but holds whenever the method under consideration is fallible. One should not indict exercise testing for these potential weaknesses, but simply recognize the problem and allow for it here as in most other spheres of medicine. Moreover, screening asymptomatic persons is not to be wholesalely decried, but rather an attempt should be made to screen more selectively; for example, choosing the deconditioned person who wishes to undergo an exercise reconditioning program, or patients with high risk occupation, such as pilots. With the burgeoning popularity of physical fitness programs, many obese, unfit persons consult their physicians about the type and intensity of exercise they might undertake. Advice given by the physician is greatly facilitated by using objective exercise testing.

To argue that stress testing is without its imperfections would be ill advised and certainly incorrect. As mentioned, all procedures have their limitations, but against these the simplicity, low cost and potentially valuable diagnostic information emerging from exercise testing permits it to stand out as among the most worthwhile aids in the assessment of the (potential) coronary patient.

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Sex and Quality of Life

ELSEWHERE IN THIS ISSUE there appears an account of sexual therapy for a couple with significant coronary artery disease. The article emphasizes the psychological and emotional aspects of their problem rather than the possible untoward effects of a bout of acute coronary insufficiency which can occur in such persons during a sexual encounter, particularly if it is vigorous. But the purpose of the treatment was to enhance the quality of life for these mature though not yet elderly persons.

It is not too long ago that an article describing any sort of sexual therapy in any degree of detail would probably not have been accepted for publication in a journal such as this—not that the

editor would have thought the readers to be prudes, but because human sexuality and the treatment of its disorders had not yet become a part of accepted general medical practice. The fact that this has now come to be the case reminds us that the content as well as the goals of medicine and patient care derive from social as well as scientific roots. During the past few years America has both been taking the wraps off of sex and developing a new goal which is described as quality of life. It is therefore most appropriate that sexual therapy to enhance quality of life becomes a part of patient care.

The times, they are a-changin', and the changes aren't all that bad!

—MSMW

Coronary Surgery in the Elderly

THE RELIEF of myocardial ischemia by surgical means is well accepted after a decade of clinical experience. The application of coronary artery bypass to individual patients requires careful consideration of risks and potential benefits of operative management as opposed to continued medical management. The issues inherent in the decision to recommend an operation are intensified in elderly patients. On the one hand, operative risks would appear to be greater. Decreased cardiopulmonary reserve, the frequent presence of advanced generalized arteriosclerosis and increased fragility of tissues tend to magnify chances for serious or fatal complications. On the other hand, relief of angina pectoris might seem less urgent in an elderly patient whose occupational and leisurely pursuits are less vigorous than a younger person's. Also considerations about prolongation of life in surgically managed patients with extensive coronary atherosclerosis[1] may appear less compelling in patients already in their eighth decade of life. Nonetheless, clinicians are faced with elderly patients incapacitated by ischemic chest pain at reduced activity levels despite good medical therapy. Moreover, the proportion of "senior citizens" in the population is increasing.

In this issue of the WESTERN JOURNAL, Tucker and his colleagues present a favorable experience with coronary bypass in patients 70 years old and older. As might be expected in this age group, clinical indications were forceful; in two thirds of the group rest angina was present, accounting for the large proportion (77 percent) of patients in whom there was involvement of all three major coronary branches. Noteworthy are the low operative mortality rate (4.5 percent), a very low perioperative myocardial infarction rate (1.5 percent; although exact diagnostic criteria are not reported), the fact that there were no perioperative strokes and the good palliative results.

The single best determinant of operative mortality in coronary artery bypass procedures is preoperative left ventricular function.[2,3] Of the patients in the authors' series there was "fair" or "good" left ventricular function in 85 percent, suggesting an appropriate concern for proper patient selection. One would like to have had hemodynamic or ejection fraction data for a more precise appreciation of this important risk factor,[4] especially in the two patients with left ventricular dysfunction who died in the hospital and who, according to the authors, "probably should not have been operated upon."

Good evidence has been provided that in experienced hands, gratifying surgical results can be obtained in the elderly, with mortality and morbidity rates equivalent to those seen in younger patients. Clinical experience of the kind documented in this report attests to the fact that cardiac aneshesia, technology of cardiopulmonary bypass, methods of myocardial protection and microvascular surgical techniques have evolved to the point of application to patients of advanced age. The message is clear: age per se should not deter or delay the decision to recommend operation for properly selected patients disabled by ischemic chest pain.

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CASE REPORTS

Refer to: Clark RA, Omenn GS: Anhidrotic ectodermal dysplasia with frequent infections and amyloidosis. West J Med 126:225-228, Mar 1977

Anhidrotic Ectodermal Dysplasia with Frequent Infections and Amyloidosis

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ANHIDROTIC ECTODERMAL DYSPLASIA is an X-linked recessive disorder in which affected males lack eccrine sweat glands and teeth, and have heat intolerance, sparse hair and a characteristic facies.[1] This condition has long been recognized, reports including a note by Charles Darwin[2] about the "toothless men of Sind": ten men in four generations in one Hindu family in Hyderabad, India, with unaffected women transmitting the disorder to their sons and with no instance of fathers transmitting the disorder to their sons. In fact, carrier females often show patchy signs of the disease such as absent or malformed teeth, irregular sweating and breast abnormalities. Expression in females is due to the phenomenon of random inactivation of the X chromosome, so that some cells express the normal gene carried on one X chromosome and others express the gene for ectodermal dysplasia carried on the other chromosome.[3,4]

The frequent occurrence of atrophic rhinitis, pharyngitis, bronchitis and pneumonia noted in affected males has been attributed to scanty mucus production and deficient ciliary action in the upper respiratory tract.[1,5,6] Additional factors, such as allergic asthma, cigarette smoking and occupational dust exposure have been implicated in some cases.[1,6,7] Cutaneous infections have not been noted in these reports.

We describe here a patient with X-linked ectodermal dysplasia and frequent cutaneous and respiratory infections, in whom certain aspects of host defense mechanisms were investigated. This case is unique in having amyloidosis and nephrotic syndrome as a complication.

Report of a Case

The index case (III-27, see Figure 1) is a 44-year-old unemployed chemist with anhidrotic ectodermal dysplasia, recurrent infections and nephrotic syndrome due to amyloidosis. The family history (see pedigree, Figure 1) shows

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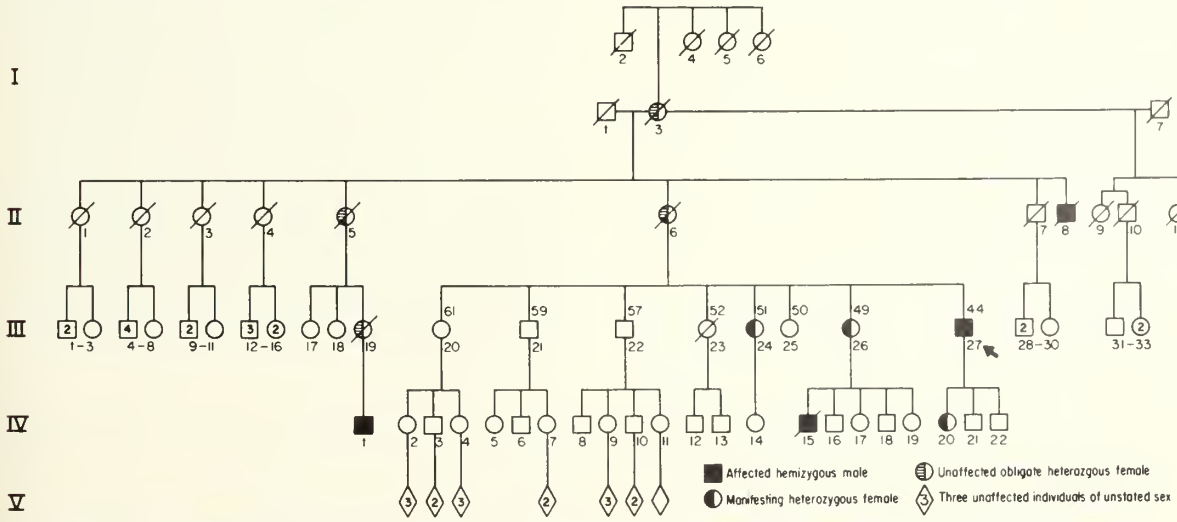

Figure 1.—Family pedigree showing typical X-linked pattern of transmission. Arrow indicates patient.

typical X-linked recessive inheritance of ectodermal dysplasia with four involved males and at least seven carrier females, three of whom have partial expression of the disease. The involved second cousin (IV-1) of the propositus was evaluated at the University of Washington Hospital in 1960 at age 21; in addition to the typical physical features of anhidrotic ectodermal dysplasia, he had allergic asthma with acute bronchospasm, recurrent pulmonary and upper respiratory infections with an acute left lower lobe pneumonia, and esophageal stenosis requiring repeated dilatation. The involved nephew (IV-15) and uncle (II-8) of the propositus were said to have frequent pulmonary infections and rhinitis. The daughter (IV-20) and one known carrier sister (III-26) of the propositus had abnormal "razorlike" teeth. Another sister (III-24) had nearly the full syndrome with sparse hair, anodontia, saddle nose deformity and anhidrosis except for scattered small patches of skin which exhibited normal sweating. She has also had recurrent respiratory infections. An additional sister (III-23) without signs of ectodermal dysplasia died at age 52 of chronic renal failure following a long history of rheumatoid arthritis.

In the propositus, recurrent purulent and atrophic rhinitis have been present since childhood. Pneumonia occurred at ages 12 and 20 and recurred several times between ages 20 and 35. Recurrent cutaneous infections began at about age 30. Over the past ten years of observation at the University of Washington Affiliated Hospitals, the following infections have been documented: November 1965—right upper lobe pneumonia; July 1966—left arm cellulitis and abscess; November 1970—cellulitis of nose following attempted surgical correction of saddle nose deformity with spread to left orbit; December 1970—herpes zoster around left eye with staphylococcal superinfection; February 1971—left shoulder cellulitis and abscess; November 1971—right middle lobe pneumonia; January 1972—superinfection of chemical burns on thighs; January 1972—bacterial cellulitis complicating third degree thermal burn on hand; November 1972—severe periorbital edema with cellulitis; November 1972—thigh abscess; December 1972—right upper lobe pneumonia; June 1973—leg ulcers infected with staphylococci; August 1973—thigh abscess; January 1975—infected leg ulcers; March 1975—right middle lobe pneumonia. The cases of pneumonia were characterized by fever, leukocytosis, pulmonary infiltrates, dyspnea and cough, but sputum production was scanty probably due to the absence of mucus glands. Sputum cultures were often not helpful, although Streptococcus pneumoniae and Hemophilus influenzae were isolated on some occasions. Pulmonary function tests done when the patient was not infected were normal. Staphylococcus aureus was cultured from cutaneous infections in nearly all instances; these responded to appropriate antibiotics, drainage and local therapy. The infections have frequently arisen in association with trauma including surgical operation, burns and self-administered parenteral medication.

Drug abuse has been a problem for 10 to 15 years and includes both oral and subcutaneous administration. Codeine and pentazocine have been the most frequently used agents, but barbiturates, meprobamate, glutethimide, chloral hydrate and methadone have been taken intermittently. Frequent psychiatric problems have arisen in relation to the drug usage. The patient is of normal or higher intelligence and is well educated. Before the drug abuse began he was a successful businessman and chemist.

Results on physical examinations when the patient has been free of infections have shown only the characteristic manifestations of anhidrotic ectodermal dysplasia, including sparse scalp and body hair, anhidrosis, depressed nasal bridge, prominent forehead, defective dentition with only a single peg-shaped tooth and normal fingernails and toenails.

Findings on analysis of urine and on serum protein determinations were normal until November 1972 when periorbital and lower extremity edema developed. Analysis of urine showed 3+ protein, but findings were otherwise normal and a 24-hour urine protein value was 5 grams. Creatinine clearance was 100 ml per minute; blood urea nitrogen (BUN), 14 mg per 100 ml; serum albumin, 2.5 grams per 100 ml and cholesterol 228 mg per 100 ml. Results on intravenous pyelogram were normal. Tests for rheumatoid factor and antinuclear antibodies were negative. A percutaneous renal biopsy (January 1972) showed extensive amyloid deposition. All glomeruli were hypocellular and distorted by large amorphous eosinophilic deposits in the mesangial regions, extending peripherally to obliterate the capillary lumens. These deposits stained metachromatically with crystal violet and were birefringent with congo red. Smaller deposits were

identified in the interstitium and in arterial and arteriolar walls. Amyloid fibrils were shown by electron microscopy (Figure 2). Treatment with furosemide, 40 to 240 mg per day, was partially successful in controlling edema. The proteinuria and hypoalbuminemia have persisted at about the same level. Hypertension (160/100) together with azotemia (creatinine, 3.3 mg per 100 ml; BUN, 61 mg per 100 ml) developed in May 1975.

Evaluation of Host Defense

Studies of host defense mechanisms are summarized in Table 1. Serum levels of immunoglobulins G, M and E were normal and IgA was somewhat elevated. Serum complement levels (total hemolytic activity and C3 by immunodiffusion) were normal. Blood leukocyte counts and differential counts were normal as was the morphology of blood and bone marrow leukocytes. Neutrophil myeloperoxidase was normal by a cytochemical technique employing benzidine.[8] Neutrophil chemotaxis was evaluated by a previously reported method[9] employing ^{51}Cr-labeled neutrophils and a standard chemotactic factor (human C5a). The response of the neutrophils was equivalent to that of normal neutrophils. Generation of serum chemotactic activity by endotoxin activation[9] was also normal. Neutrophil iodination was studied by a modification of a previously described method.[10] The reaction mixture contained normal serum, zymosan as the phagocytic particle, ^{125}I and either normal or patient neutrophils. The normal response observed indicated intact phagocytosis, metabolic activity and myeloperoxidase activity. T-lymphocyte function was not evaluated, although the spectrum of infectious agents observed in the patient does not suggest an abnormality in this area.

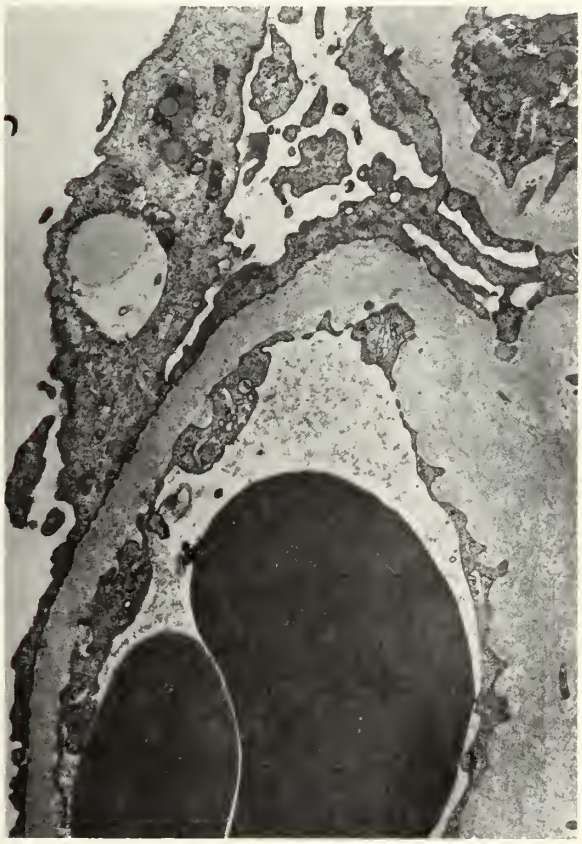

Figure 2.—Electron micrograph of a peripheral glomerular capillary loop. The foot processes are fused. There is a small mass of fibrils on the epithelial aspect of the glomerular basal lamina and in the adjacent subendothelial region. The largest mass of fibrils can be seen on the right. These fibrils have the size, distribution and location of amyloid fibrils. X22,400. (Micrograph provided by Dr. Gary R. Striker)

Discussion

In the patient reported here there is a typical family history, physical examination and clinical history for X-linked anhidrotic ectodermal dysplasia. Although most reported cases have been in infants and children, numerous adults are known with this disorder, having survived with great care to avoid high environmental temperatures and to control high fevers. The unusual features of this case are the numerous and varied infections and the eventual development of amyloidosis and nephrotic syndrome.

There is no history of allergic asthma or occupational dust exposure, in this patient, but some of the infections, particularly the episodes of cellulitis, were clearly related to subcutaneous self-

TABLE 1—*Studies of Host Defense Mechanisms**

Test	*Patient*	*Normal*
Immunoglobulins		
IgG (mg/100 ml)	1600	600-1700
IgA (mg/100 ml)	640	50-300
IgM (mg/100 ml)	140	50-200
IgE (U/ml)	128	25-300
Complement		
CH_{50} (units)	142	80-162
C3 (mg/100 ml)	165	120-170
Neutrophil Function		
Myeloperoxidase	Present	Present
Chemotaxis†	..	..
Cell response	101.5%	>70%
Serum activity	73.3%	>70%
Iodination‡	73.9	40-80

*See text for methods and explanations.
†Percent of normal control.
‡Nmoles/10^7 cells/hour.

administration of drugs. He was not known to have injected agents intravenously. No abnormalities in neutrophil function or levels of serum complement or immunoglobulins were detected. The patient's infections appear most likely related to local factors such as the abnormal epidermal and epithelial barrier rather than to a systemic defect in phagocytic or immune mechanisms. Although frequent respiratory infections have been noted in other patients with anhidrotic ectodermal dysplasia,[1,5,6] the occurrence of multiple cutaneous infections has not been described.

Amyloidosis with nephrotic syndrome is a recognized complication of chronic inflammatory conditions including dermatoses. In a review of 100 cases of systemic amyloidosis, eight were associated with cutaneous disorders.[11] The dermatoses included hidradenitis suppurativa, stasis ulcers of 25 years' standing, psoriatic arthritis, recurrent basal cell carcinoma, dystrophic epidermolysis bullosa and three cases of lepromatous leprosy.

The patient's family history is interesting because of the examples of partial expression in female carriers. In fact, one sister has all of the major manifestations of anhidrotic ectodermal dysplasia. The development in another sister of renal failure in association with chronic rheumatoid arthritis raises the interesting possibility of amyloidosis in another family member, although medical records could not be obtained for confirmation.

Summary

A patient is described with anhidrotic ectodermal dysplasia, frequent cutaneous and respiratory infections and amyloidosis with nephrotic syndrome. The increased susceptibility to infections appeared to be related primarily to local factors since phagocytic and immune function were intact. Amyloidosis, a previously unreported complication of anhidrotic ectodermal dysplasia, probably developed as a consequence of the recurrent infections.

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Refer to: Cohen IM, Vieweg WVR, Alpert JS, et al: Osteogenesis imperfecta tarda—Cardiovascular pathology. West J Med 126:228-231, Mar 1977

Osteogenesis Imperfecta Tarda

Cardiovascular Pathology

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OSTEOGENESIS IMPERFECTA TARDA is a rare inherited disorder of connective tissue characterized by skeletal, ocular, cutaneous, otologic, dental and internal abnormalities. It is related to such conditions as Marfan's syndrome and pseudoxanthoma elasticum. In contrast to the other inherited disorders of connective tissue, valvular heart disease has rarely been documented by cardiac catheterization in patients with osteogenesis imperfecta tarda. In McKusick's review of more than 100 cases of osteogenesis imperfecta tarda, two patients were judged to have aortic regurgitation on clinical grounds.[1] Criscitiello and co-workers in 1965 reported the cases of three patients with aortic regurgitation.[2] Cardiac catheterizations were not done although one case came to postmortem examination. Recently, five cases of valvular heart disease in patients with osteogenesis imperfecta tarda have been evaluated in the cardiac catheterization laboratory.[3-5] In three patients aortic regur-

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gitation was noted and in two mitral regurgitation was found to be present.

The purpose of this report is to describe the cases of two patients with osteogenesis imperfecta tarda and aortic regurgitation confirmed by cardiac catheterization. Findings in these patients are compared with those in previously reported patients.

Reports of Cases

CASE 1. In a 17-year-old Mexican-American man an avulsion fracture of the right tibial tuberosity occurred while he was preparing to leap from a crouched position. There was a history of four previous extremity fractures which occurred without trauma and which required surgical correction. Neither parents nor siblings had blue sclerae. However, two children of the patient's siblings (3 and 4 years of age) had blue sclerae, but no history of fractures. There was no personal or family history of hearing loss and findings on an audiometric test done upon entrance to active military service had been within normal limits. A heart murmur was discovered in conjunction with this hospital admission. There was no personal or family history of heart disease, including rheumatic fever, and the patient said he had had no cardiac symptoms or chest trauma.

On physical examination the patient was seen to be short and thin, with a triangular shaped head. The blood pressure was 130/60 mm of mercury and the pulse was 76 beats per minute. Blue sclerae were present. The teeth were deformed but not translucent. Bounding carotid pulsations were present. The left pectoralis major muscle was absent. A systolic ejection murmur and thrill were present over the aortic area and along the left sternal border. A grade III/VI blowing decrescendo diastolic murmur was present along the left sternal border. A third heart sound was present.

Findings on a roentgenogram of the chest were normal. On an electrocardiogram prominent left ventricular voltage was shown. An echocardiogram showed no abnormalities. Findings on roentgenograms of the long bones included mild osteoporotic changes in the distal femur and proximal tibia bilaterally as well as thinning of the cortex and increased trabeculations in the distal radius bilaterally. On roentgenograms of the skull notable prominence of the occiput without basilar indentations was noted.

At cardiac catheterization right and left heart

TABLE 1.—*Comparison of Clinical and Cardiac Catheterization Data Among the Seven Reported Cases*

AUTHORS	*Case 1 Cohen*	*Case 2 Cohen*	*Heppner*	*Case 1 Wood*	*Case 2 Wood*	*Case 1 Weisinger*	*Case 2 Weisinger*
Age	17	39	32	49	52	20	51
Severity of osteogenesis imperfecta	5 fractures	30 fractures	Severe	Multiple fractures	Multiple fractures	Three fractures	Multiple fractures
Hemodynamic data (mm Hg)							
Right atrium	6	....	6	....	....	Normal pressures	No data
Right ventricle	28/6	....	26/6	57/27	No data	Normal pressures	No data
Pulmonary artery	28/14	....	28/7	....	....	....	No data
Mean	18	....	....	....	No data	....	....
Wedge mean	10	....	....	22	No data	....	....
Left ventricle	110/8	150/16	146/12	115/15	....	....	.../21
Aorta	110/70	144/88	....	125/60	No data	....	174/56
Cardiac output (liters/minute)	4.5	....	9.2	....	....	....	....
Cardiac index (liters/minute/meter^2)	3.4	....	3.49	....	....	....	....
Aortic regurgitation	3 to 4+	1+	1+	None	None	Severe	Severe
Mitral regurgitation	None	Minimal	None	Considerable	Severe	None	None
Aortic root dilatation	None	None	Marked	None	None	Marked	Mild

pressures were normal (Table 1), and there was no systolic gradient across the aortic valve. The ventriculogram on the left side was normal without evidence of mitral valve prolapse. The aortic valve was not calcified but 3+ aortic regurgitation was shown by aortic root cineangiography. The aortic root was not dilated and a tricuspid aortic valve was noted.

CASE 2. In a 39-year-old white woman cardiac catheterization and coronary angiography were carried out because of the recent onset of chest pain consistent with the diagnosis of unstable angina pectoris. The diagnosis of osteogenesis imperfecta tarda had been established in childhood because of the occurrence of multiple (more than 30) atraumatic fractures associated with deep blue sclerae and delayed wound healing with exuberant scar formation. There was no history of hearing loss, chest trauma, rheumatic fever or infectious endocarditis. The patient's father had had a myocardial infarction at age 52. An uncle also had blue sclerae, but no unusual fractures or hearing loss.

On physical examination the patient was seen to be thin and shorter than average in stature. The blood pressure was 140/90 mm of mercury and the pulse was 88 beats per minute. Blue sclerae were noted. The teeth were translucent, but not deformed. Carotid pulsations were normal. A faint Grade I/VI diastolic blow was heard at the upper left sternal border. There were no systolic murmurs, third or fourth heart sounds.

On a roentgenogram of the chest several old rib fractures and a normal cardiac silhouette were seen. Results on a resting electrocardiogram were normal.

Selective coronary angiography gave entirely normal findings. Left sided pressures are shown in Table 1. The ventriculogram on the left side showed no abnormalities except for prolapse of the anterior leaflet of the mitral valve. Aortic root cineangiography showed 1+ aortic regurgitation. The aortic root was not dilated and a tricuspid aortic valve was noted.

Discussion

Both aortic and mitral regurgitation have been shown angiographically to be present in patients with osteogenesis imperfecta tarda.[3-5] However, aortic regurgitation would seem to occur more commonly than mitral regurgitation in this entity. Table 1 compares the available angiographic and hemodynamic findings in the seven patients (including the present cases) in whom cardiac catheterization has been carried out. Age at onset of symptoms varies considerably and there appears to be no good correlation between the severity of skeletal manifestations of osteogenesis imperfecta and the incidence or severity of cardiovascular abnormalities. Aortic regurgitation can range from mild to severe and there may or may not be associated dilatation of the aortic root. Dilatation of the mitral annulus and redundancy of the mitral valve leaflets are also occasionally seen.

Aortic Valve and Root Pathology.

Although osteogenesis imperfecta tarda is considered to be an inherited, generalized disorder of connective tissue, the cause of aortic regurgitation may be either dilatation of the aortic root or intrinsic aortic valvular abnormalities. A "true" aneurysm lined with continuous endothelium was noted in a leaflet of an otherwise normal mitral valve in a patient with severe aortic regurgitation.[2] Aneurysm of the sinus of Valsalva (without histologic characterization) was described by Heppner[3] in another patient with aortic regurgitation. The sinuses of Valsalva and aortic annuli were dilated and the aortic cusps elongated and thin in the two patients of Weisinger and co-workers.[5] Cystic medial mucinous or myxoid degeneration of the aortic valve and proximal ascending aorta was noted in two patients who underwent aortic valve replacement,[5] and this was presumed to be the pathological lesion in Heppner's patient[3] despite a normal renal arterial biopsy. Changes consistent with cystic medial necrosis were found on postmortem examination in the aortic wall of one of Criscitiello's[2] patients.

Mitral Valve Pathology.

Both dilatation of the mitral annulus and redundancy of the mitral valve with chordal rupture have been described at postmortem examination in patients with osteogenesis imperfecta tarda.[4]

Aortic and mitral valve replacement have been accomplished in patients with osteogenesis imperfecta. A bleeding diathesis and delayed wound healing with a tendency toward disruption of suture lines were anticipated. However, aortic valve replacement in the two patients reported by Weisinger was carried out successfully and without postoperative difficulty.[5] Similarly, a benign course was noted in two patients in whom mitral valve replacement was done.[4] In each of the latter two cases, however, friable tissues were

noted at the time of valve replacement, therefore making the procedure technically more difficult.

As noted above, the severity of the bone disease and the severity of the valvular disease are not necessarily concordant. Intuitively, one might expect that in patients with osteogenesis imperfecta and many fractures, more severe cardiovascular pathologic conditions might develop than in those who have had fewer fractures. However, it is evident from Table 1 that severe aortic regurgitation can occur in patients with fewer fractures. Conversely, patients with many fractures may have only mild aortic regurgitation. Age seems to have little effect on the severity of valvular lesions. We conclude that in patients with all degrees of osteogenesis imperfecta, severe cardiovascular abnormalities can develop which affect the aortic root and valve more frequently than the mitral valve. Valve replacement is technically feasible, and the clinical results are satisfactory in such cases.

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Refer to: Robbins AL, James CF, Nash DF, et al: Poisoning involving improperly stored parathion. West J Med 126: 231-233, Mar 1977

Poisoning Involving Improperly Stored Parathion

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PESTICIDES, especially of the highly toxic organophosphate variety, are prominent among causes of poisoning in children. Many of these cases involve transfer of the pesticide from its original container into a container a child associates with food and drink; or improper storage allowing a child ready access to the pesticide.[1-3] This report describes a recent case of the latter kind involving parathion and illustrates a cooperative effort between a physician and an analytical laboratory with pesticide and pesticide metabolite analytical capability. Exposure history, diagnosis, treatment and excretion of metabolites are presented.

Report of a Case

A 4-year-old girl, sleeping with her mother, awakened at about 3 AM with some respiratory distress and a low-grade fever. The girl's mother, thinking that a recent cold with fever and vomiting had returned, gave her aspirin. The child made her way back to her own bed and the mother noticed that the little girl was wobbly on her feet. The mother heard nothing further from her during the night. At 9 AM she went to see why the child had not wakened and found her comatose, febrile and having a great deal of trouble breathing. An ambulance was called and the child was taken immediately to a local hospital.

On admission the patient was comatose and unresponsive to stimulation by pinprick or pinching. Rectal temperature was 39.2°C (102.6°F), pulse was 120 and regular and respiration was 52 and labored. Muscular twitching involving the face, neck and upper extremities was noted. There was no evidence of head trauma or other physical injury. Examination of the patient's eyes showed pinpoint, equal and round pupils which were unresponsive to light or accommodation. A gross vertical nystagmus was also present. Findings on examination of the ears were normal. Copious mucousy oral secretions were noted with no evidence of intraoral trauma. Rhinorrhea was also noted. The patient's neck was supple, with

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no apparent discomfort on motion. No adenopathy was noted.

Examination of the chest showed there to be increased inspiratory effort throughout. Coarse rhonchi were scattered throughout with no rales. Cardiac examination showed a pronounced sinus tachycardia with a rate of 120 and no gross murmurs.

The abdomen was soft with diminished bowel sounds, and an obviously distended bladder extending up to the umbilicus was noted. The bladder was catheterized. The genitalia were normal.

Deep tendon reflexes were symmetrically depressed. Toes were down going.

While the examination was proceeding, ambulance personnel were examining the patient's homesite where they noted that a paper sack of 25 percent wettable powdered parathion had fallen to the ground in an adjacent garage and broken. The patient and her brother and sister had been playing in the powder. With this information, and clinical features consistent with organophosphate poisoning, 1 mg of atropine was given intravenously. The patient immediately became calmer, and began to breathe more easily, the copious secretions diminished and she became semiresponsive. Her pupils remained pinpoint, however, and in 20 to 30 minutes she began to slip back into a comatose state. A second milligram of atropine was then given intravenously and good improvement was again noted but with residual muscular tremors. On advice of a toxicologist 0.5 gram of pralidoxime chloride (Protopam Chloride®) was given slowly over 1½ hours. Immediate improvement was noted and, with the exception of some drowsiness, the patient was asymptomatic by 12:30 PM. She was released from the hospital five days after admission. The mother was contacted two weeks after the precipitating incident and she reported that no further problems were experienced by the child.

Laboratory Findings

Samples of blood, urine and gastric washings were taken. The blood was separated into plasma and red blood cells and analyzed, respectively, for pseudocholinesterase and acetyl cholinesterase activity using the pH Stat method which is a continuous automatic titration of the acetic acid formed by the action of cholinesterase on acetyl choline substrate at constant temperature. Enzyme activity is expressed as micromoles of substrate hydrolyzed per minute per ml of sample.

Cholinesterase values show the typical prompt response to treatment with pralidoxime chloride (Protopam® Chloride) of organophosphate poisoning. These results are shown in Table 1.

The two principal metabolic pathways for parathion in the human are shown in Figure 1. Both parathion and its oxidation product paraoxon are powerful cholinesterase inhibitors.

Exposure to parathion can thus be confirmed by analysis of urine for the end metabolic products shown: diethyl thiophosphoric acid (DETP), diethyl phosphoric acid (DEP) and p-nitrophenol (PNP). Accordingly, a specimen of the patient's urine was analyzed for DEP and DETP by the method of Shafik and co-workers[4] and for PNP by the method of Cranmer and co-workers.[5] Results of the analysis are shown in Table 2.

Examination of the table shows steadily declining values of DETP. Values for PNP, however, show a second peak in the samples taken on May 23 and May 24. A similar pattern appears to hold for the DEP excretion. These are shown graphically in Figure 2.

Much the same pattern of PNP excretion was reported by Arterberry and associates in 1961.[6] No analysis for DEP was possible at that time.

Gastric washings were negative for ethyl parathion. This is possibly due to the exposure being primarily dermal although some ingestion had apparently also occurred. The possibility also exists that the period of several hours from the last possible ingestion to admission to the hospital may have been long enough to allow the pesticide to clear the stomach.

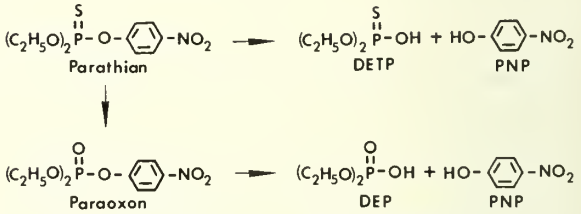

Figure 1.—Metabolism of parathion. DETP = diethyl thiophosphoric acid, DEP = diethyl phosphoric acid, PNP = p-nitrophenol.

TABLE 1.—*Serial Cholinesterase Determinations*

	Micromoles/minute-ml	
	Plasma	*Red Blood Cells*
5/21 Before Protopam	0.21	0.95
5/21 After Protopam	0.52	6.18
5/22 24 hours after Protopam	0.72	6.54

Normal Adult Values: Plasma = 2.4-6.6; RBC = 12.0-16.7

Discussion

In retrospect, it appears that the illness suffered by this child two days before the poisoning episode was likely a mild poisoning. The two other children, in whom symptoms did not develop, had also been playing in the parathion powder. Their exposure was evidently only dermal and their evening bath probably prevented the development of clinical symptoms. The patient had also been bathed and the bathing probably prevented a much more serious poisoning.

This poisoning follows an altogether too typical pattern of pesticide poisoning in children. Improper storage of highly toxic materials, allowing access by children, is clearly the cause of this episode. These preventable poisonings will likely become more common as the organophosphate and carbamate pesticides replace the increasingly banned, but generally less toxic, chlorinated compounds unless a strong public education program is mounted relative to proper storage and handling of pesticide materials. It also appears to be essential that practicing physicians become acquainted with the symptoms of this type of poisoning so that prompt diagnosis may be made and appropriate treatment may be started as soon as possible.

TABLE 2.—*Analysis of Urine*

		Values in Parts per Million		
Date	*Time*	*DETP*	*DEP*	*PNP*
5/21/75	?	3.88	0.47	3.76
5/22/75	2:00 pm	0.72	0.30	0.89
5/23/75	1:10 pm	0.37	0.35	1.37
5/24/75	8:00 am	0.19	0.27	1.32
5/25/75	8:00 am	0.19	0.15	0.55
5/26/75	7:30 pm	0.11	0.07	0.26

DETP = diethyl triophosphoric acid
DEP = diethyl phosphoric acid
PNP = p-nitrophenol

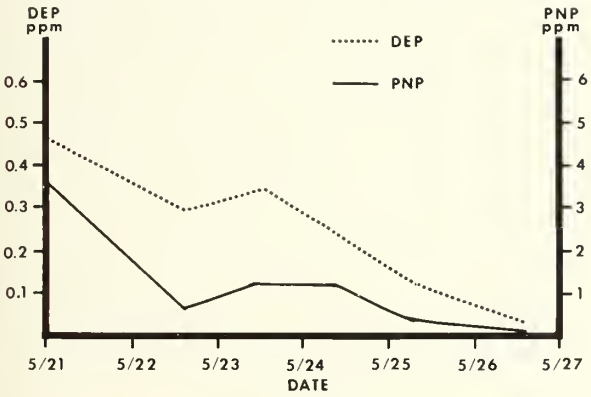

Figure 2.—Urine analysis. DEP = diethyl phosphoric acid, PNP = p-nitrophenol.

Although is is beyond the scope of this report to present a detailed description of differential diagnosis and treatment of organophosphate poisonings, it is appropriate to summarize the principal clinical symptoms of various degrees of poisoning by organophosphate compounds.

- *Mild poisoning:* anorexia, headache, dizziness, weakness, anxiety, tremors of tongue and eyelids, miosis, impairment of visual acuity.
- *Moderate poisoning:* nausea, salivation, lacrimation, abdominal cramps, vomiting, sweating, slow pulse, muscular tremor.
- *Severe poisoning:* diarrhea, pinpoint and nonreactive pupils, respiratory difficulty, pulmonary edema, cyanosis, loss of sphincter control, convulsions, coma, heart block.

Exposure routes may be oral, dermal or by inhalation, and symptoms generally appear within half an hour to three hours after exposure, but rarely beyond 12 hours.

Confirmation of the diagnosis of organophosphate insecticide poisoning may be made by the laboratory tests described in this report.

Detailed discussions of the pharmacology and toxicology of pesticides may be found in several references.[7-10]

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Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgment before publication.

Health Care Not an Industry

To the Editor: By conceding, as was done in an editorial in the December issue (Another "War" for Independence? West J Med 125:490-491, Dec 1976), that our health care system is an "industry," the wedge is provided through which a premise is validated and its providers are disadvantaged. It is such usage that fits the current effort in Oregon of those intent upon state regulation of hospital rates. They have singled out private sector hospitals as "obviously an industry . . . [to which] application of statistical generalizations as applied to industrial [sic] efficiency" is proposed.

Several decades ago, the late Morris Fishbein and the Pennsylvania Supreme Court (in a ruling against hospital strikes) both noted that a hospital is not an industry. Times have, of course, changed. Nevertheless, the term "industry," as applied to hospitals, would make sense only when applied to that fraction of about 14 percent of the 7,000 hospitals in the United States that are investor owned.

Lest we imprison ourselves dangerously in the economic viewpoint, the debate about the phrase "health industry" will not be about the fact that there is a business side of health care but about values and dedicated professionalism. The latter concept, I hope, does not exist only as a kind of abstraction. It adds to the incentive of altruism and aids to controvert the unsavory implications of more frequent modern allusions to health care as commercialism.

This is not to be construed as a simple condemnation or downgrading of the vital importance of the financial side of health care. It is a plea for its realistic recognition as a subsidiary necessity of everyday life in a complex modern situation. Moreover, the business side of health care is not the commonplace variety of business. It is a variant whose variance is bottomed upon ethical and humane considerations, not the dollar sign. Too much emphasis on economics in health care places its providers in greater political jeopardy.

Needless to say, it is proper and timely that we organize for another "war" for freedom from an overbearing bureaucracy. Your call for such action is commendable. Let's hope we don't all wait for George to do it.

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Lake Oswego, Oregon

Distribution of Medical Care

To the Editor: Your editorial regarding change in the coming century [Medicine and the certainty of change in the coming century. West J Med 126:62-63, Jan 1977] hits the nail on the head.

I am most interested when you mention the problems regarding "attempts to achieve a fair and even distribution of this success to the public."

While I was president of the AMA I tried to emphasize the necessity of providing a more even distribution of medical care. I still believe that group practice with satellite offices in neighboring small towns which can be served by different group members on specific days, with a local nurse or physician's assistant who can serve emergencies would do two things: (1) provide medical care in communities that are not now being served and (2) give each physician the opportunity of belonging to a group of his peers rather than being solely responsible for the health care of a community.

Of course some doctors prefer being the medical king of an area, but this is not generally true of today's young physicians. They need the comfort of colleagues and the opportunity for continued education, daily and periodically in depth.

I also advocated in 1970 and 1971 that the

output of physicians by our medical schools be doubled by 1980. I think that we have accomplished this, so we no longer need to rob foreign countries of their young doctors. However, most of the increase here will stay in the big cities—too bad!

Congratulations on the expansion of THE WESTERN JOURNAL OF MEDICINE.

WALTER C. BORNEMEIER, MD
Past President
American Medical Association
Saratoga, California

A Physician's Assistant Responds

TO THE EDITOR: In the December issue is a letter by Dr. Frank Z. Reade discussing physician's assistants.

Dr. Reade states that some physician's assistants give the impression to patients that they are doctors, yet the law which regulates physician's assistants plainly states that each patient who is seen by a physician's assistant must sign a consent form that states the patient realizes he is being seen by a physician's assistant. Also, the law states that a physician's assisant must wear an identification badge stating the assistant's name and the title "Assistant to the Primary Care Physician," when rendering medical services.

It is against the law for a physician's assistant to call himself a doctor. It is also against the law for persons who have not finished an approved program to call themselves physician's assistants. If Dr. Reade has come in contact with some of these persons, I suggest that he report the incidents to the California Board of Medical Quality Assurance.

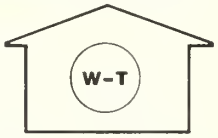
Concerning malpractice, a member of the Physician's Assistant Examining Committee of the Board of Medical Quality Assurance informed me that there have been no cases of malpractice brought against physician's assistants in the state of California.

The use of properly supervised physician's assistants is a way in which doctors can increase the quality of health care and increase the number of patients served. And no one is more interested in maintaining the integrity of this new profession than are physician's assistants themselves. We are interested in informing doctors and the public about the laws governing physician's assistants and the value they have.

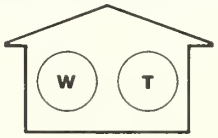
JAMES HANKS III, PA-C

The House of Medicine

TO THE EDITOR: Once upon a time doctors cared for patients and also taught their colleagues and students. Some worked well and some worked badly. Some taught well and others taught badly. But all had a duty both to work with patients and to teach. The house of medicine, thus, was one. Let us illustrate this schematically:

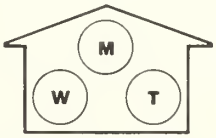


Medicine being a conservative profession, this edifice persisted over the centuries virtually unchanged. That is, until the dawn of the 1900's when a few doctors split away from their working colleagues. They began to teach a lot more than they worked with patients. These men so impressed a certain Mr. Abraham Flexner that he launched a crusade to institutionalize their existence. Thus was academic medicine born. And thus the house of medicine came to know two inhabitants:



Over the years, these working doctors and teaching doctors lived in more-or-less peaceful coexistence in their respective towns and gowns. But then a stranger appeared. Lacking in personality, he became known as the third party, and he paraded in a multitude of guises. Strangely, he was not always welcome. Strange because he sought only to transfer money into the coffers of the house of medicine.

Painfully aware was this third party that he was not a physician himself. Yet he took his own work seriously. Honesty compelled that measurements involving the transfer of his money be made. Thus was the *measuring* doctor, the steward of the third party's funds, born; a doctor, because only doctors know how to measure what doctors do. So now the house of medicine knew three:

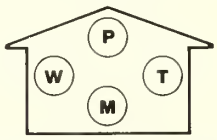


The third party grew stronger and richer. He transferred more and more funds. And he demanded ever more measurements. Soon it became

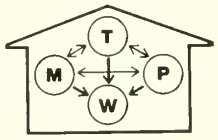
clear that there was much more to measure than the transfer of funds. One could also measure how the workers worked, and how the teachers taught. The measuring doctor learned to do both.

But the task grew even more complex. Teaching doctors began to teach the measurers to measure just as the measurers first taught the teachers how to teach and the workers how to work.

Yet the third party was still not satisfied. Not a doctor himself, he began to worry that the workers, teachers and measurers might become friends. And that their ardor for working, teaching and measuring might diminish in the glow of good fellowship. The solution was clear: the policing doctor quietly appeared. And the house of medicine came to know four:



The house became crowded, and it became difficult to breathe. Nonetheless, all kept busy. The teachers taught everyone. The measurers measured everyone. And the police policed everyone. The workers simply worked.



The anatomy and physiology of the house of medicine were difficult to comprehend, even to its own inhabitants. Demanding explanations, the third party also became restless; transfers of funds now came reluctantly and with ill will.

Medicine's inhabitants looked over their shoulders with increasing alarm. Their activities grew more frenzied. Workers worked harder. Teachers taught harder. Measurers measured harder. And police policed harder. The walls bulged and the roof threatened to burst. The inhabitants fought for space and air. The third party tapped his foot impatiently.

It was the workers who first noticed the disequilibrium of arrows. They complained but, outnumbered and out-arrowed, there was little they could do. Taught, measured and policed, they still continued to work—as well as could be expected.

Unhappy with all, however, the third party now brandished his funds and stamped his foot. The inhabitants were startled. Some ran towards the third party. Others huddled together in fear. Holes appeared in the walls of the house of medicine and winds blew through the holes.

Still, the house stood. Trembling, the remaining inhabitants worked on the walls. Gradually and ever so carefully, they also began to examine one another. More virtue than evil met the eye. The light of good fellowship glimmered, then gleamed. Work resumed, but more calmly—teaching, more quietly; policing, more gently; measuring, more carefully.

The third party never was satisfied.

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Refer to: Scalzi CC, Loya F, Golden JS: Sexual therapy of patients with cardiovascular disease. West J Med 126: 237-244, Mar 1977

Special Article

Sexual Therapy of Patients with Cardiovascular Disease

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Physical illness or disability inevitably has a damaging effect on sexual relationships. Physicians are usually unaware of the sexual consequences of illness on their patients, and lack experience in treating sexual dysfunctions.

The report of treatment of a couple with serious cardiovascular disease illustrates the potential efficacy of brief sex therapy for improving the quality of a patient's life. If a primary physician lacks the skills to conduct sex therapy, he may collaborate with nonphysician therapists. The physician's knowledge of the physiological and psychological effects of a specific illness on his patient is essential to successful therapy. Often, simple education, encouragement or reassurance by the physician is enough to overcome the damaging effects of illness on a patient's sex life.

SEX THERAPY has flourished in the past decade, stimulated by basic research[1,2] and a social climate in which public attention has focussed on human sexuality. The brief, behaviorally oriented approaches to sexual dysfunctions[3,4] are based on the concept that they are caused by sexual ignorance, performance anxiety and culturally influenced inhibition. It is widely known that sexual dysfunctions are more frequently caused by psychogenic problems than by physical disease. This knowledge has resulted in a justifiable enthusiasm for treating the psychogenic sexual dysfunctions. Unfortunately, sexually dysfunctional patients who are physically ill and disabled have been virtually ignored.

It is now generally recognized that illnesses such as diabetes mellitus, chronic renal failure and multiple sclerosis are frequently associated with enough nervous or vascular damage to cause permanent impairment of sexual functioning. Some attention has recently been directed toward the organic causes of erectile failure in men and inhibition of sexual pleasure in women.[5,6] Studies of patients with spinal cord injuries have contributed to our awareness that even severe physical disabilities do not preclude some forms of satisfactory sexual functioning.[7,8]

However, many health care professionals are not aware of the enormous impact on sexual func-

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tioning that any illness may have. The extent of sexual disability is staggering. Part of the oversight may be a consequence of the myth in our culture that sick people are not sexual. We have a tendency to designate as nonsexual certain categories of people. This is shown in our attitude toward the aged, the mentally retarded and the very young.

Another reason for the oversight is the discomfort of the physician concerned. He or she may have information on human sexuality and sex therapy but may feel uncomfortable asking patients about sexual problems. If one identifies a sexual complaint but has no knowledge of how to treat it, one may be prevented by embarrassment from taking a sexual history.[9] In some instances, a health care worker may contribute to a sexual dysfunction by neglect. Neglecting to discuss a patient's sexual concerns or problems affected by an illness, injury or disability may result in unnecessary morbidity.[10,11] Urologists who do prostatectomies have observed that postoperative erectile failure is diminished if patients are preoperatively given positive expectations about their ability to achieve erections.[12] In this we see how health care professionals may approach sick or disabled persons with a cardiovascular ailment in an effort to identify and ameliorate sexual dysfunctions caused by the illness. The case to be presented illustrates how a couple experienced a greatly prolonged period of abstinence and dysfunction due in part to their physician's failure to discuss the sexual implications of both their cardiac problems.

Report of a Case

George, 55 years old, and Mary, 60 years old, have been married for 22 years. They have had no children together, although each had a child in a previous marriage. Mary worked in a semiskilled job but is now retired. George is currently awaiting a decision concerning his return to his job as a foreman-supervisor at a factory. Judged by levels of education, occupation and income, the couple's socioeconomic status is estimated to be within the upper portion of the lower class. Both George and Mary have an extensive history of coronary artery disease. In a medical follow-up visit George's erectile failure was disclosed, and the couple was referred for treatment to the authors (C.S. and F.L.). A thorough evaluation gave the following information:

Mary's history of coronary disease dated back 11 years to the occurrence of her first myocardial infarction. She convalesced six months before returning to work and normal physical activities. Some eight years later, Mary had a second and more severe myocardial infarction while at home in her husband's presence. She was advised to retire from her job. After nine months, during which sexual activity was prohibited, she was allowed to resume a limited schedule of all activities. Mary also lost weight (30 percent) and this was accompanied by transient symptoms of depression. These physical and psychological conditions remitted within 18 months of the second myocardial infarction. However, two years later Mary's coronary artery disease exacerbated, requiring surgical operation for coronary bypass. During the recovery period she lost more weight and depression and numerous psychosomatic complaints (such as musculoskeletal pains) occurred. She became acutely aware of any pain or physical change she felt in her body. This hypersensitivity to her own somatic sensations has persisted as the primary sequela of her illness. As could be anticipated, Mary's preoccupations included worry and fear about the physical condition of her husband.

Significantly, Mary neither asked about reinstituting any type of sexual activity nor did any of her physicians advise or educate her in this regard. In her own estimation, sex was within the domain of "normal activities." As a direct result, she did not permit herself any sexual activity until her physician said that she could resume "normal activities."

Approximately a year after Mary's bypass operation, George had a myocardial infarction. On angiography extensive coronary artery disease not amenable to surgical intervention was found. George has been treated medically in the year since the myocardial infarction; however, he has not been permitted to return to work. As was true for Mary, George recalled no advice related to the continuation or possible modification of sexual activity at any time following his illness. On one of his follow-up visits, specific assessment of sexual functioning disclosed a history of consistent erectile failure since his myocardial infarction.

Many detailed questions were asked about the specifics of the dysfunction and the role the couple played in contributing to the maintenance of their own undesirable sexual behavior. For

George and Mary, the cause of the erectile failure appeared to be directly related to the coronary artery disease that affected both marital partners. Before Mary's first myocardial infarction, they reported no sexual difficulties. Their frequency of intercourse was approximately three times a week, each partner was orgasmic, neither had extramarital sexual interests or activities, and both were satisfied with the quality of their sexual and marital relationships. Following Mary's infarction 11 years ago, they were able to recall a slight change in George's desire for sexual activity. He did not seem to initiate lovemaking quite as often. They both agreed that between Mary's first and second infarction, the frequency of intercourse decreased to two times weekly. Although George and Mary were able to provide this information when asked, they were only partially aware of its occurrence as it was taking place. No masturbation or extramarital sexual contact was initiated by either partner during this time. They had never talked to one another about their developing sexual difficulties.

They became more aware of changes in their sexual behavior after Mary had her second myocardial infarction. No sexual activity occurred for the nine months Mary was recovering. It was resumed at a frequency of once to twice a week. In addition, George began to notice a change in his attitude and feeling toward sexual intercourse with his wife. It should be recalled that Mary's second infarction occurred in George's presence while they were both lying in bed. Also of importance are the hypochrondriacal sequelae that Mary carried with her from the life-threatening illnesses she had experienced. They served as a personal reminder of the severity of Mary's physical condition, the weight she had lost, the apathy of her spirit and even the fragility of life itself. The sum of these factors made George feel guilty for still wanting to have sexual intercourse with his wife.

Further history uncovered actual fears and fantasies of George's physically hurting Mary during the act of sexual intercourse. The typical position they used was the male superior position where George would be required to place the weight of his body directly on Mary. George would picture in his mind how gravely ill and depleted Mary appeared during her illness. He would then be repulsed by his own amorous thoughts of intercourse, and feel guilty for wanting to follow through with his sexual desires. Consequently, he refrained from engaging in their normal frequency of sexual activity.

These undesirable attitudes were magnified following Mary's open heart surgical operation several years later. Mary convalesced for eight months and during this time no sexual activity occurred. When intercourse was attempted, it was experienced as painful for Mary and subjectively interpreted by George as a further confirmation of his fears and fantasies of damaging Mary's fragile health in the satisfaction of his own sexual needs. The therapists' assessment of the painful intercourse suggested that George's fears may have manifested in the form of attempting to "get it over" as quickly as possible. Therefore, Mary may not have been stimulated to the point that adequate lubrication occurred.

Mary's coronary artery disease appeared to contribute to George's erectile dysfunction which occurred approximately 50 percent of the time. In a separate interview with George, the male therapist discovered that George began his first extramarital affair as his erectile difficulty worsened. He participated in the affair several times a month and experienced only occasional erectile failure in his efforts to reestablish his competence with a new partner.

The final event of etiological significance was the myocardial infarction that George had had approximately a year following Mary's operation. George was almost completely unable to get an erection from this time forward. He would have occasional morning erections but could not act quickly enough to have intercourse before the erection became flaccid. The couple presented themselves for sex therapy about four months after George's myocardial infarction.

Many of George's previous fears of hurting Mary now took on even greater significance because he had experienced a myocardial infarction and could directly share the feelings associated with a life-threatening illness. Although his post-infarction treatment prescription included maximum physical exercise, he still harbored doubts about his ability to withstand the rigors of sexual intercourse. Fears of suffering a "coital coronary" were not limited to George. Mary knew her heart was enlarged. Sexual activity caused it to beat faster and she could feel its pounding against her chest. She was afraid the more forceful beating would cause her heart to enlarge even more and endanger her life. Similarly, she often expressed the fear that the pressure of George's body dur-

ing intercourse would cause her "chest stitches to burst."

George now found himself faced with many of the same doubts, fears, anxieties and uncertainties that Mary had had for the preceding several years. The difference was that Mary expressed her feelings and attitudes directly while George worried and tried to keep them contained in hopes of avoiding feelings of self-pity. However, the opposite result seems to have occurred—that is, Mary experienced some degree of relief while George appeared to become more anxious. In no instance would either engage the other in an open discussion of their fears and anxieties around their coronary artery disease or their sexual dysfunction.

It became clear that the sexual dysfunction was closely related to fears and fantasies surrounding their coronary artery disease. The sexual history elicited the specific cause but did not unearth the full magnitude of their fears and concerns. The couple was referred for treatment of erectile failure to a male-female co-therapy team consisting of a psychology intern and a clinical nurse specialist. The co-therapists were trainees supervised by a psychiatrist experienced in sexual therapy.

Course of Sexual Treatment

Initial evaluation

Before a couple is accepted for treatment a thorough assessment is made:

- The specific nature and history of the sexual dysfunction is established. Detailed questions are asked about previous and present sexual functioning and the specific behaviors associated with the sexual symptom.
- It is determined if there is any severe psychopathology in either partner (for example, schizophrenia or severe depression) which might interfere with the couple's ability to participate in treatment.
- The quality of the relationship between the couple is evaluated. If it is too unstable and hostile, that would also preclude treatment.
- Medical evaluation is made of any physical disability because it might contribute to sexual dysfunction.

The common sexual difficulties experienced by men with cardiovascular disease are erectile failure (impotence) or retarded or premature ejaculation. Women with cardiac disease suffer from inability to achieve orgasm or generally diminished sexual pleasure. The results of George's and Mary's evaluation indicated the sexual dysfunction to be erectile failure. No major psychopathology was evident in either partner and their marital relationship was quite amicable. Results of medical evaluation did not preclude either partner from participating in their normal range of sexual behaviors.

Both George and Mary at first responded to the evaluation sessions with skepticism, caused by fear that nothing could be done to help them. The therapists were sensitive to these concerns, which patients commonly have. They expressed optimism that the erectile difficulty could be successfully treated. This initial anxiety is often related to the new patient's anticipation of reexperiencing the erectile failure in the therapy situation.

Steps of Treatment

Sensate Focus: Nongenital

The first task of therapy is to remove the pressure to produce, perform and achieve. This is accomplished by banning all sexual activities not specifically assigned as part of the treatment. The rationale is to divert attention away from arousal, erection, intercourse and orgasm. In their place are substituted the alternative behaviors of giving and receiving the pleasure without the anxiety of having to produce or perform.

The next step is to begin sensate focus exercises designed to provide the couple with the opportunity to give and receive pleasure by experimenting with different ways of stroking, touching and caressing themselves and each other. Because sex therapy encourages discovery of one's own pleasurable sensations, each partner is freed of the expectation that he or she must produce a singular "adequate response." Furthermore, the therapists have given *permission* for, and asked the couple to become more aware of their own pleasurable feelings and sensations.

Frequently, initial sensate focus exercises begin with the process of patients "getting in touch with their own bodies" by discovering various kinds of pleasurable, neutral and nonsexual sensations. Emphasis is directed toward these "new" pleasurable body sensations rather than the more familiar sensations of sexual arousal associated with intercourse and orgasm.

The following steps used to treat George and Mary are typical of sex therapy:

Session 1

A body exploration in front of a full-length mirror and genital exploration with a hand mirror was assigned. This exercise was employed in response to their reported lack of awareness of their own bodies. Some degree of anxiety and discomfort was anticipated and discussed with the couple. It was emphasized that anxiety is common among couples who have not engaged in such contact, or when sex has been primarily oriented toward orgasm and performance.

Session 2

It was clear that they were uncomfortable with the genital exploration. At this point a decision was made not to try to overcome their uncomfortable feelings. Rather, an alternative exercise with the same goal was assigned. The couple was asked to stimulate their skin with ten different objects to explore and discover new pleasurable body sensations and possibly expand their sexual repertoire.

George enjoyed the assignment and stated that the sensations made him feel "real sexy." Mary enjoyed it somewhat less. She did not like being nude and felt ashamed of her body. The educative process of sex therapy encourages the expression of these and other uncomfortable feelings in an effort to help the couple understand the fears and concerns often motivating their feelings. As Mary's negative feelings were explored it became very clear that her discomfort and anxiety were related to her fear that she was no longer attractive and sexually appealing to her husband. George's reassurance that he did not see her as less attractive seemed to reduce some of her anxiety.

Sessions 3 and 4

Mutual body massages excluding the breasts and genitals were assigned. Since the couple had successfully explored and discovered new pleasurable sensations individually and had begun the process of communicating their feelings, it was appropriate to add additional dimensions to the sexual exercises. They were given sensate focus exercises which emphasize mutual giving of pleasure and also communication. They were given very specific instructions about the setting, how to relax before doing the assignment, and various ways of caressing and touching. Special emphasis was placed on explaining the purpose of the giver and receiver roles. For example, if George were receiving the massage, he was to concentrate on the pleasurable sensations and to tell Mary what he liked as well as what he did not like.

Sessions 5 and 6

Usually at this stage a program of sex therapy would have dictated full body massages including genitals and breasts. However, several issues regarding physical health interrupted the normal course of treatment. Specifically, George was scheduled for heart catheterization to determine the need for open heart surgical operation. Both George and Mary were extremely anxious about it and not able to communicate their fears to one another. Therefore, these sessions were used to explore their individual and mutual fears.

The therapists became aware of George's level of anxiety when he asked a series of questions related to the upcoming catheterization. The responses did not reduce his anxiety. At this point, more direct questioning showed his fears of an operation and imminent death. His underlying apprehension was due to the uncertainty of the prognosis. With each additional test, it seemed more likely that he would be unable to return to his previous level of activity. It became more apparent that George was basing his expectation of a cardiac surgical procedure on Mary's experience and her long, arduous convalescence from her operation. More specifically, he was afraid that, like his wife, he too would become physically incapacitated and emotionally preoccupied with the cardiac disability.

Mary's major concerns came from her experience as a cardiac patient. She was afraid that George would undergo a perilous series of operations and, ultimately, not survive. To a woman who had grown very dependent on a strong healthy husband, the thought of a complicated surgical operation and his possible death were extremely frightening. Through discussions of the pending operation, George and Mary were shown that they shared many of the same concerns. This was the first time in their marriage that George had discussed an important problem with his wife. Much to his surprise, she did not break down; to the contrary, she was very supportive. The usual sexual homework assignments were suspended during this time and the couple were instructed to continue these discussions at home as their assignment.

Sensate Focus: Genital

This next series of exercises is designed to allow each partner to give pleasure to the other through massage and genital caressing. As with previous sensate focus exercises, emphasis is placed on identification of feelings and sensations by the person receiving the massage and communication to the partner who is in the role of giver. In this manner, the receiver is able to know what types of stimulation are pleasurable and, just as important, is able to request and guide the efforts of the giver. Again, the couple is instructed to concentrate on sensations rather than efforts to achieve ejaculation or orgasm.

Sessions 7 and 8

Full body masages, nongenital and genital, were assigned but only partially completed. The presence of a hematoma in George's femoral area, a complication of the heart catheterization, proved to be another physical setback that was of primary concern to them. Initially, George expressed anxiety and frustration from the swelling and pain caused by the hematoma. He was reassured that the hematoma was a common complication and encouraged to consult his physician for specific measures to relieve the pain.

At this point, the therapists consulted George's physician to ascertain the physical limitations that could interfere with the progress of sex therapy. This was the belated beginning of a liaison between physician and sex therapists that proved to be quite helpful. The physician was informed and involved in the sex therapy plan to insure coordination with the medical treatment plan. He was eager to consult and support the sex therapy efforts by reassuring George and Mary that the hematoma was healing satisfactorily and the specific sexual exercises would not be harmful.

The couple reported a good experience with the nongenital massage and were instructed to proceed to a full body massage including the genitals. George reported feeling aroused and did finally experience an erection that was partially inhibited by pain from the residual hematoma. He was now able to associate this pain with his underlying fear that a full erection would cause the hematoma to burst. This is an excellent example of how pain associated with fear can result in a learned sexual dysfunction.

Intervention consisted of clarifying their misconceptions about the hematoma and providing factual information that reduced their fears. This illustrates the importance of identifying the underlying fears, and the efficacy of simple education in the sex therapy of patients with physical problems.

Session 10

The couple was asked to repeat the genital massage. Pain from the hematoma was subsiding and George was able to carry out the assignment and enjoy a full erection. He reported little pain and, more important, minimal fear as a direct result of factual information given during the previous session.

Erectile Response

George had now experienced a return of erectile responsiveness. The emphasis of sex therapy shifted to the restoration of a consistent, reliable erection. With the remittance of the sexual symptom came a sense of confidence and desire to strengthen the revitalized erectile response.

The usual series of exercises assigned to promote control over erection and retarded or premature ejaculation are extravaginal orgasm and vaginal containment without orgasm. Extravaginal orgasm consists of each partner bringing the other to orgasm without intercourse. Manual and masturbatory stimulation are substituted for intercourse. Vaginal containment of the penis without the goal of orgasm is introduced as the final step before active intercourse. The male is instructed to insert his erect penis into his partner's vagina. The female is instructed to be a passive participant in that she is "lending her vagina" to her partner and following his requests and directions for movement which will allow the male to achieve further penile and ejaculatory control.

These exercises are optional and employed typically if initial erections are less than full and consistent. They are very important steps in the treatment of premature ejaculation and retarded ejaculation.

Session 11

A full body-genital massage bringing each partner to orgasm was assigned. In an effort to promote confidence in George's ability to achieve regular erections, therapy focused on orgasm through manual stimulation. In the past, they had only experienced orgasm through intercourse. Their initial response to this exercise was guarded. It was necessary to explain that this form of sexual behavior was "normal." Successful completion of the masturbation exercises illustrates

the importance of giving the patients permission to engage in sexual behaviors which may be new for them.

Session 12

As it became obvious that George had control over erections, the couple was given the option of proceeding to intercourse and orgasm. The reason this was presented as an option rather than an assignment was to minimize anxiety associated with resumption of intercourse. They elected this option and were delighted with their ability to achieve orgasm in coitus as they had before. Had this assignment been unsatisfactory, vaginal containment without orgasm would have been assigned.

Session 13 and 14

Development of a maintenance program was begun. The purpose of a maintenance program is to insure that the new sexual behavior becomes a part of the couple's sexual repertoire beyond the termination of treatment. The first step was to ask each partner to list desirable sexual and nonsexual behaviors that they would like to see continued. The next step involved a mutual discussion of how they could implement and maintain the desired behaviors on their own. The final step was to meet with the physician and the couple to review the specific problems and progress achieved in sex therapy. This also served to transfer the authority and responsibility back to their primary physician to monitor future sexual adjustment.

Discussion

The application of sexual therapy in the treatment of sexual dysfunction in a couple with coronary artery disease illustrates several points:

- Health care professionals largely are still unaware of the enormous impact that physical illness may have on sexual functioning. Moreover, the attitude that sick people are not sexual appears to play a major role in the perpetuation of this nescience.
- Health care professionals may inadvertently contribute to a patient's sexual dysfunction by neglecting to discuss the impact of physical illness on sexuality.
- The lack of sexual information may contribute to the development of a patient's fears about the deleterious effects of sexual activity on health. A common result is an unnecessary and prolonged abstinence from sexual functioning.[10,11]
- All patients develop idiosyncratic fantasies about their body's functioning when they become ill or disabled. Whether the concern is about a hematoma bursting, or a suture line which may dehisce, the physician needs to learn about the fantasy in order to dispel his patient's misconceptions.

The sexual dysfunctions of patients with coronary artery disease can be divided into those that are primarily psychogenic and those that are physically caused. Psychogenic sexual dysfunctions include those cardiovascular conditions in which there may be minimal physical impairment of sexual functioning. Myocardial infarction, recovery from coronary bypass surgical operation and angina are the major examples represented in this category. Such psychogenic sexual dysfunctions appears to result from fear of death or injury during coitus. With some modification, the sexual therapy outlined in the case presentation may serve as a model for the treatment of psychogenic sexual dysfunctions. For example, a modification for a patient recovering from a coronary bypass operation would include experimentation with sexual positions that impose less stress on the coronary vascular system and reduce postoperative pain. For a patient with angina, identification of less strenuous sexual positions and activities as well as the prophylactic use of nitroglycerine may be appropriate.

Sexual dysfunctions due to cardiovascular disease that have primarily physical causes include femoral occlusive disease, cardiomyopathy, severe valvular disease and congestive heart failure. These conditions are frequently associated with enough nervous or vascular damage to permanently interfere with normal sexual functioning. The more debilitating the disease, the greater the need for more radical modifications in treatment of the sexual dysfunction.

For example, a patient with severe femoral occlusive disease may be unable to achieve and maintain an erection. One should not assume that the absence of an erection precludes alternative forms of sexual arousal and pleasure. To the contrary, sick people can be sexual. Modifications in sex therapy for physically disabled patients begins with an assessment of their physical limitations and capabilities. This information is shared with the couple and specific sexual exercises are assigned to expand their sexual repertoire. In many cases, both partners may be orgasmic or

achieve a significant degree of pleasure despite the erectile dysfunction. They are encouraged and given permission to explore and become more aware of the pleasurable feelings and sensations that remain available to them. Some degree of mutual gratification can be achieved despite physical limitations. The importance of careful assessment of physical limitations and capabilities in relation to sexual functioning cannot be over emphasized. Patient education, permission giving, facilitating communication skills and support provided by the therapists are the primary tools used to ameliorate a wide variety of sexual dysfunctions. These same methods can also be used more positively by concerned health care professionals to prevent dysfunctions before they occur.

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Corticosteroids for Treatment of Infectious Mononucleosis

When are corticosteroids indicated for treatment of infectious mononucleosis? First of all, I have to tell you there is no proven efficacy. However, there are ample anecdotal stories, and most experts, even in the absence of documentation, would use steroids for impending airway obstructions resulting from severe pharyngitis or the pain of the pharyngitis itself (if that were severe); severe thrombocytopenic purpura, acute hemolytic anemia and the severe neurologic syndromes. Some would also say if the leukopenia were severe, they would also add steroids as well. Again, there are no controlled studies that show proven efficacy.

—RICHARD P. WENZEL, MD, *Charlottesville, VA*
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Regionalization of Perinatal Care in Orange County, California

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IN JANUARY 1975 the Orange County (California) Medical Association sponsored a symposium on regionalization of perinatal care in Orange County. At the time of this meeting it appeared that many physicians were confused, threatened and often antagonized by the concept. The purpose of this paper is to examine the problem of regionalization in Orange County, with the thought that the situaton in this area may serve as a model for other areas.

Overview of Obstetrical Care in Orange County

The Orange County Health Planning Council has published a significant amount of information necessary to an understanding of the obstetrical care problem in the county. In 1973 there were 22 hospitals with obstetrical facilities in Orange County. From 1960 to 1973 there was a 25 percent decline in the birth rate in the United States. During that same time in Orange County there was a 45 percent decline in the birth rate. In 1970 there were 25,506 births in Orange County. In spite of the large increase in population in Orange County, the number of births was down to 22,729 by 1973. The birth rate in the county fell from 17.9 in 1970 to 14.0 per thousand population in 1973. In 1973 there were five facilities in each of which there were more than 1,000 live births in Orange County. In four of the five there were more than 2,000 live births. Eleven facilities accounted for fewer than 600 deliveries each per year. The five facilities with more than a thousand births accounted for more than 50 percent of the total births in the county. There are two certified neonatal intensive care units in the county at this time. The two units are the University of California, Irvine, Medical Center and the Children's Hospital of Orange County.

Critical Problems and Physicians in Private Practice

Although many hospitals claim that obstetrics is a losing proposition financially, most still do not want to give it up. The reason for this is mainly the fear of losing lucrative gynecology since many physicians find it convenient to do all their work in one location. This partially explains why in 1973 there was a 43.9 percent obstetrical occupancy rate in Orange County and in spite of this low occupancy rate, construction to provide 80 more beds was under way at the end of 1973. Of interest is that federal standards for obstetrical occupancy rate is at least 75 percent occupancy. In summary, one of the things that has to be examined is the question of how a hospital can give up obstetrics without fear of losing income from gynecology.

The question of staff privileges at a regional center is another point of controversy. This may be a great source of anxiety, particularly for general practitioners providing obstetric or pediatric care. Safeguards for these physicians must be established to ensure that they are allowed to continue practicing. It seems likely that this problem could be resolved by establishing a close working

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Presented at Symposium on Regionalization of Perinatal Care in Orange County, Orange County Medical Association on January 18, 1975.

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relationship between the primary physician and consulting obstetrican, perinatologist or neonatologist. A system can be designed in which a patient understands that her doctor is still taking care of her but that a consulting physician may also be involved.

Social and religious aspects of regionalization are another source of anxiety. For example, obstetricians may be concerned about the situation of a high-risk patient who desires postpartum sterilization either at the time of cesarean section or immediately following delivery in a regional center which for religious reasons does not allow sterilization. There appears to be a great deal of resistance among many obstetricians concerning delivery of high-risk patients where there is no opportunity to do postpartum sterilization. Their argument is further strengthened by the fact that in high-risk mothers there often is a strong medical indication for sterilization.

Another concept that has to be explored is the question of whether there is a minimum number of births necessary before a regional center can be established. There are some excellent hospitals in Orange County that do not have 2,000 or more deliveries per year. Representatives from these hospitals feel that they have the necessary facilities and that in due time they indeed would build up their census. They ask why their hospitals should be penalized now, and never be given an opportunity to develop into regional centers. They feel that in the future they could attract obstetricians from other hospitals and build up a sizable census. This argument is a sound one and this is the way some centers will evolve.

One subject that deserves close attention is the economic factors involved in regionalization. It is well known that a hospital chosen as a regional center probably will be the recipient of large amounts of money both from the government and private philanthropic sources. The physician himself may find that third party payment for high-risk pregnancies may be contingent upon delivery at a regional center. Since all pregnancies are potentially high risk, it is not difficult to envision third party payment only when a baby is delivered at a regional center. Another financial aspect that should be considered is the large amount of money that will be necessary to pay for continuous obstetrical anesthesia coverage, for a neonatologist and for the sophisticated equipment and maintenance of this equipment. It would seem likely that only a regional center with a large volume and perhaps extra income from private and governmental sources would be able to maintain such services and equipment.

In some states, regionalization has been forced by the state by selectively licensing hospitals based on certain guidelines. The fact that hospital obstetrical and pediatric sections require periodic review for relicensure may prove to be a strong force in the regionalization program in this county.

The final question that must be discussed concerning regionalization is perhaps the one provoking most anxiety. Physicians are concerned about who picks the center, where it will be and how many others there will be. The answer is that no one picks the center. The administration of a hospital in each community will have to decide that it will lead the way by upgrading the hospital's facilities according to prescribed guidelines. This should in effect draw physicians from other surrounding hospitals with inferior facilities and consequently a center will develop. Superimposed upon this natural evolution of a center might be the state's refusal to relicense some smaller hospitals with lesser facilities.

Results of the OCMA Questionnaire

The Orange County Medical Association, in cooperation with the Orange County Obstetrical and Gynecological Society and the Orange County Pediatric Society, submitted a questionnaire to all practicing obstetricians, pediatricians and family practitioners in the county. A total of 600 letters were sent out, of which at least 237 were answered. Each respondent was asked to indicate whether he practiced pediatrics only or obstetrics only, or whether he was in general practice providing obstetric services with or without pediatric care. The last category was general practitioners providing pediatric care only (Tables 1 through 7).

- *Question 1. Are you in favor of setting up one hospital in each region or community where you would do all your deliveries?*

Replying in the affirmative were 113 physicians, replying in the negative were 79.

The obstetricians as a group were very much in favor of such a plan, with 59 for and only 14 against. The pediatricians were almost equally divided, with 25 for and 19 against. The general practitioners were somewhat negative with 16 for and 25 against among the general practitioner-obstetricians and with 12 for and 21 against among those general practitioners providing pediatric care only.

TABLE 1.—*Are you in favor of setting up one hospital in each region or community where you would do all your deliveries?*

Total Yes	113	*Total No*	79
Pediatrics Only		*OB Only*	
Total Yes	25	Total Yes	59
Total No.	19	Total No	14
GP-OB		*GP-Peds*	
Total Yes	16	Total Yes	12
Total No	25	Total No	21

- *Question 2. Are you in favor of full-time obstetrical anesthesia coverage which would be essential to such a center?*

Across the board the respondents strongly endorsed such a concept. In all, 179 were for this proposal and only 29 against it. Among the pediatricians 50 were for it and only 2 against it. Among the obstetricians, 70 were for and there were 5 against it.

TABLE 2.—*Are you in favor of full-time obstetrical anesthesia coverage which would be essential to such a center?*

Total Yes	179	*Total No*	27
Pediatrics Only		*OB Only*	
Total Yes	50	Total Yes	70
Total No	2	Total No	5
GP-OB		*GP-Peds*	
Total Yes	28	Total Yes	34
Total No	11	Total No	9

- *Question 3. Are you in favor of a full-time obstetrician, pediatrician and/or perinatal specialist with commitment to high-risk perinatal care to be available for consultation at all times?*

In this case the answer was overwhelmingly yes, with 201 for and only 25 against. Among the pediatricians, 63 were for and only 3 against. Among the obstetricians 66 were for and only 8 against.

TABLE 3.—*Are you in favor of a full-time obstetrician, pediatrician and/or perinatal specialist with commitment to high-risk perinatal care to be available for consultation at all times?*

Total Yes	201	*Total No*	25
Pediatrics Only		*OB Only*	
Total Yes	63	Total Yes	66
Total No	3	Total No	8
GP-OB		*GP-Peds*	
Total Yes	32	Total Yes	41
Total No	7	Total No	7

- *Question 4. Are you in favor of at least one full-time neonatal specialist with 24-hour coverage for high-risk deliveries?*

This concept was heartily endorsed, with 192 for and 33 against. Among the pediatricians, 58 were for and 8 against. Among the obstetricians, 67 were for and 7 against.

TABLE 4.—*Are you in favor of at least one full-time neonatal specialist with 24-hour coverage for all high-risk deliveries?*

Total Yes	192	*Total No*	33
Pediatrics Only		*OB Only*	
Total Yes	58	Total Yes	67
Total No	8	Total No	7
GP-OB		*GP-Peds*	
Total Yes	29	Total Yes	38
Total No	11	Total No	7

- *Question 5. Are you in favor of fetal monitoring to be carried out on most patients in labor?*

A total of 158 respondents were for this and 57 were against. Of the pediatricians, 56 were for, and only 6 were against this proposal. The obstetricians had 53 for and 21 against.

TABLE 5.—*Are you in favor of fetal monitoring to be carried out on most patients in labor?*

Total Yes	158	*Total No*	57
Pediatrics Only		*OB Only*	
Total Yes	56	Total Yes	53
Total No	6	Total No	21
GP-OB		*GP-Peds*	
Total Yes	24	Total Yes	25
Total No	1	Total No	16

- *Question 6. Are you concerned about a possible weakening of the traditional physician-patient relationship?*

In all, 111 of the respondents felt that there was a cause of concern in this regard and 117 felt there was not. Among the pediatricians 23 were concerned, 38 were not concerned. Among the obstetricians 34 were concerned and 41 were not concerned. Among the general practitioner-obstetricians 29 were concerned and 15 were not. Among the general practitioner-pediatricians 25 were concerned and 23 were not.

TABLE 6.—*Are you concerned about a possible weakening of the traditional physician-patient relationship by such a program?*

Total Yes	111	*Total No*	117
Pediatrics Only		*OB Only*	
Total Yes	23	Total Yes	34
Total No	38	Total No	41
GP-OB		*GP-Peds*	
Total Yes	29	Total Yes	25
Total No	15	Total No	23

- *Question 7. Should regional centers be open to all physicians practicing obstetrics and pediatrics?*

The reply in this case was rather one sided. Of the respondents, 196 said yes and only 29 said no. Among the pediatricians 54 said yes, 11 said no. Among the obstetricians 64 said yes, 11 said no. Among the general

practitioners practicing obstetrics 38 were in favor of this, one was against. Among the general practitioners practicing pediatrics 40 were in favor of open centers and 6 were against.

TABLE 7.—*Should regional centers be open to all physicians practicing obstetrics and pediatrics?*

Total Yes	196	*Total No*	29
Pediatrics Only		*OB Only*	
Total Yes	54	Total Yes	64
Total No	11	Total No	11
GP-OB		*GP-Peds*	
Total Yes	38	Total Yes	40
Total No	1	Total No	6

There were many written comments and some of the more frequent replies have been summarized. In response to the first question concerning the acceptance or rejection of a regional center, most physicians said they favored the concept of a regional center. However, many felt confused as to how you define a regional center, how big the region should be, what areas are involved and how many centers there would be. As to the second question concerning full-time obstetrical anesthesia, again most people liked the idea. Of particular concern is the fact that soaring malpractice insurance costs have prompted some anesthesiologists to reconsider full-time obstetrical anesthesia coverage.

In regard to the third and fourth questions concerning the availability of perinatal and neonatal specialists for consultation, most respondents were favorably inclined provided that it was made clear to the patient that the consultant only consulted and that the primary physician was still managing the case. In response to the question of fetal monitoring to be carried out on most patients in labor there were several comments. Some felt that fetal monitoring was necessary only when indicated. Others felt that it was causing unnecessary cesarean sections. Some physicians were concerned that permanent records of monitoring could result in subsequent litigation if an unusual pattern was noted in a child in whom a physical or mental problem later developed.

Question number six inquired as to concern about a possible weakening of the traditional physician-patient relationship by such a program. Here there was a great deal of comment. There was concern about full-time physicians and nurses and about possible friction as to who exercises ultimate control over the patient. Many stressed the point that privileges for all physicians bringing patients to regional centers must be guaranteed. One general practitioner who practices obstetrics and pediatrics said, "We must resist regional programs, they are another lock on the door of the practice of medicine as we know it." Another physician put it another way, "Consultants should remain consultants and clearly identifiable as such." Another physician answered the question this way, "Leave me alone." In short, there was a good deal of anxiety concerning the traditional physician-patient relationship if this program goes into effect. Physicians were worried that they would lose their patients and that they would lose control and management of patients—in short, that they would lose their independence.

The final question was: "Should regional centers be open to all physicians practicing obstetrics and pediatrics?" Nearly everyone agreed that this should be true, although many replied that physicians should be qualified to practice in these places by virtue of boards, board eligibility or proven practice experience. Many felt that continuing education programs would close any gaps. General practitioners most of all were extremely concerned about this. One suggestion was to write it into the bylaws that primary physicians should always be in charge and that they would call consultants as needed, which is essentially the way it is done at present. Another physician felt that centers should be open to everyone but with regular performance reviews. Some indicated that in cases of high-risk pregnancy, they would refer the patient to a specialist anyway. Many stressed that policies should be made with all practicing clinical physicians in the community represented, and that this should include general practitioners. A general practitioner practicing only pediatrics put it this way, "The concerned hospitals together with the Orange County Medical Association should guarantee the qualified physician the right to practice in the center in his region." A few physicians were very concerned that there was, as one said, "no single way to protect ourselves in keeping a center such as this open to all." Some felt that this was opening the door to socialized medicine. A general practitioner practicing obstetrics and pediatrics put it this way, "Privileges must be based on provable capability, not specialty society membership. Family physicians should be monitored by qualified family physicians until approved. Obstetricians should be monitored by obstetricians until skill is demonstrated." Some people thought that the whole business was non-

sense because in most cases patients do not require care in sophisticated treatment centers. It is true that 90 percent of deliveries are routine but unfortunately we have no way of identifying in advance most of those mothers or babies in whom difficulties will develop. As long as this is a fact then every patient must be considered high-risk and centers used for delivery.

Summary

In summary, after reviewing the results of this questionnaire, it is apparent that the physicians in Orange County are in favor of the best possible pediatric and obstetrical care available. Some feel that a regional center will not improve care. Many feel that such a situation would destroy the traditional physician-patient relationship. Most feel that if such centers are established, they must be open to all physicians. Many have voiced grave concern that this would give an entree to socialized medicine.

After talking to many people and studying the data, it is the authors' opinion that certain concepts must be accepted if regionalization of perinatal care is to become a reality in Orange County. A system must be designed in which private practitioners are guaranteed the right to practice in such a center. All administrative controls must come ultimately from those in private practice. Reviewing should be by peer review of other practitioners. Both consultants and patients must clearly understand who the primary physicians are and that the consultants are no more than that. Many of the respondents also have emphasized that governmental control should be left out of this system. It should be understood from the beginning that any funds from government should not have any strings attached which might jeopardize control by the practicing physicians themselves. If such assurances can be given, we think that there will be no reservations about this concept of regionalized care in Orange County.

Mesenteric Venous Thrombosis and the Pill

The thing that worries me about mesenteric venous thrombosis is that it's been reported in young women taking contraceptive pills . . . It's a very serious problem and I should suggest that in any woman taking contraceptive pills who's having severe bouts of recurrent pain, one might suspect at least the possibility that it's related to this process. It has an insidious onset. It has a very poor survival rate because frequently it's not picked up early enough. And it's frequently associated with rather serious diseases anyhow.

—HARRIS R. CLEARFIELD, MD, *Philadelphia*
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BOOK REVIEWS

THE WESTERN JOURNAL OF MEDICINE does not review all books sent to it by the publishers. A list of new books received is carried in the Advertising Section.

DOCTORS AND PATIENTS—Robert S. Smith, MD, FACS. Syms-York Company, PO Box 7158, Boise, Idaho (83709), 1976. 163 pages, 14 illustrations, $8.00.

This delightful book should be of interest to all who have had the privilege of practicing medicine in the Western states. It tells the experiences of a young surgeon who joined the medical community at Boise, Idaho, 40 years ago. It also communicates the deep satisfaction that comes with private practice as it relates to other doctors and as it relates to the personal contact with private patients. Not only are the day-by-day happenings of the past detailed but the book also presents a picture of changes in present day medicine. As a closing theme it gives a prophetic glimpse into what the practice of medicine will probably be like in the future.

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ADVANCES IN MEDICAL COMPUTING—Proceedings of the Third International Symposium on Computers in Medicine—Edited by J. Rose, PhD, FRIC, MBIM, FIL, F InstCSc, MI EnvSc, College of Technology and Design, Blackburn; and J. H. Mitchell, MD(Glas), MRCP(Ed), MRCP(Glas), D Obst RCOG, M InstCSc, Consultant Physician, Paisley. Churchill Livingstone Medical Division, Longman, Inc., 19 West 44th St., New York City (10036), 1975. 189 pages, $29.50.

This volume contains an introductory address, 20 papers, and a few pages of questions and replies arising in discussion: the whole being the proceedings of the Third Triennial International Symposium on Computers in Medicine, held in Blackburn (England). The theme of the symposium was "how can the computer be of assistance to medical personnel in their work?" Under this broad topic, projects are described involving computer diagnosis (using straightforward Bayesian methods), signal processing, clinical data systems and management information systems. The description of the volume appearing on the dust cover states that "it incorporates the latest advances and results obtained *in situ* and is not based on esoteric thinking or theoretical approaches." This may be a bit overoptimistic, and the reader may wonder where *in situ* really is. The program consisted of 29 contributions from the United Kingdom, 5 from the United States, and 1 from Sweden.

Professor Scadding's insightful introductory paper on the classification of diseases discusses some of the pivotal issues that distinguish medical computing from computerized account-keeping. While not eschewing the "esoteric" or "theoretical" he correctly identifies (according to this reviewer) some of the important conceptual difficulties. The approaches that others (such as Lamson and Pratt) have made toward some of his objectives are unfortunately omitted. One paper discusses the organization of computing facilities for clinical laboratories and introduces the reader to some of the general features involved in planning such computing systems. Much of the specific advice relates to British resources or practice. The papers dealing with the computer diagnosis of acute conditions within the abdomen and of jaundice may be of interest to clinicians wondering about the application of computers to diagnosis in specialty care. Descriptions of specific computer applications in clinical laboratories, for electrocardiographic analysis and for radiotherapy planning reflect conventional practice utilizing mini-computers. The anecdotal accounts of system acceptability and difficulties are as interesting and perhaps as valuable as the data on system design.

Papers on data systems for use in general practice, and in outpatient clinics reflect the principle that the success of a data system depends more on the energy and enthusiasm of the developer than upon the technology.

This book will appeal to readers who would have liked to attend the symposium itself. It may be of interest to general readers curious about computers in medicine, but unwilling to browse through the periodical literature. It does not fill the continuing need for suitable texts for students, nor was it intended to do so.

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RECENT ADVANCES IN CLINICAL PSYCHIATRY—Number Two—Edited by Kenneth Granville-Grossman, MD(Lond), FRCP, FRCPsych, Consultant Psychiatrist, St. Mary's Hospital, London. Churchill Livingstone Medical Division, Longman, Inc., 19 West 44th St., New York City (10036), 1976. 358 pages, $38.00.

The key words in the title of this book suggest that its readers will come away enriched with *new* information, of value in understanding and *treating* psychiatric syndromes. The book's preface states that its purpose is to "present a discerning account of recent developments, particularly in relation to previous knowledge and current practice." If that is what the reader expects he will be disappointed. In fact, most of the chapters deal with information from five to 15 years in print. They will be of interest chiefly to researchers and teachers, and they are rarely germane to the needs and opportunities of clinicians. The volume costs $38: over a dime a page, including the index.

So much for the caveat about the misleading title. However, among the book's 11 chapters are several which constitute competent and up-to-date *reviews* of important areas of psychiatric investigation and practice. Desmond Kelly's section on neurosurgical treatment of psychiatric disorders is a model of what a monograph should be: lucid, balanced, critical and explicit enough to allow the reader to draw his own conclusions about key issues. It also shows that a contention-ridden issue can be evaluated dispassionately by someone with sufficient scholarship and forbearance. While some would argue that the studies Kelly cites in support of the value of psychosurgical intervention are more severely flawed methodologically than he believes, the judiciousness of his conclusions and the excellence of his summary of fronto-limbic physiology alone would make the chapter valuable.

C. M. Tonks contributes a rewarding monograph on differential aspects of psychiatry in the female, with a good discussion of recent studies of premenstrual syndromes, postpartum depression and the psychological consequences of therapeutic abortions. The evidence cited adequately supports Tonk's skepticism about the nosological reality of premenstrual tension and of postpartum psychoses, and also justifies the conclusion that routine psychiatric screening of women voluntarily seek-

ing abortion is not necessary because the risk of serious emotional disturbance following such procedures is "slight."

The chapter on marital breakdown by S. Crown makes little effort to deal with "recent advances," but it does provide a satisfactory summary of many of the treatment approaches currently employed for marital discord, and it contains a brief survey of the epidemiological and social variables that may contribute to recent changes in the patterns and the rates of marital breakdown. While the studies reported in Crown's chapter are mostly from Great Britain, the findings are usually applicable to American populations.

Flor-Henry's monograph on epilepsy and psychopathology begins with an excellent historical review of changing beliefs about the "epileptic personality," before bogging down in a rather idiosyncratic system for relating the sites of electrical disturbances in the brain to coarse diagnostic groupings such as neurosis, personality disorder, schizophrenia and depression. Less adequate is the chapter on behavior therapy which lacks (as does the index) a single mention of biofeedback theory and technology. Maybe biofeedback, which is almost synonymous with "recent advances" in the western United States, has not yet captured the attention of our British colleagues. I found the chapter on clinical psychopharmacology disappointing; it does not reflect recent work relating drug concentrations in formed blood elements (rather than serum) to clinical effects and toxicity. The monograph on social factors in mental illness depends excessively on survey studies vintage 1950-1960, and neglects consideration of recent studies on life change events and their relationship to mental illness.

This is an expensive book, not quite what its title suggests, and quite uneven from section to section. It is not a good choice for a practicing clinician trying to stay current in his office practice. For teachers and researchers some chapters will be useful, and for their sake the book deserves space in institutional if not private libraries.

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MEDICAL MICROBIOLOGY—The Practice of Medical Microbiology—Twelfth Edition: Volume II—Robert Cruickshank, CBE, MD, FRCP, FRCPE, DPH, FRSE, Hon LL D(Aberd), Professor Emeritus of Bacteriology, University of Edinburgh; J. P. Duguid, MD, BSc, FRC Path, Professor of Bacteriology, University of Dundee; Consultant in Bacteriology, Tayside Health Board; Consultant Advisor in Microbiology, Scottish Home and Health Department; B. P. Marmion, MD, DSc, FRC Path, FRCPE, FRSE, Professor of Bacteriology, University of Edinburgh; Chief Bacteriologist, Royal Infirmary, Edinburgh; and R. H. A. Swain, MA, MD, FRCPE, FRC Path, FRSE, Reader in Virology, University of Edinburgh; Consultant in Virology, Royal Infirmary, Edinburgh. Churchill Livingstone Medical Division, Longman, Inc., 19 West 44th St., New York City (10036), 1975, 588 pages, $22.00.

The subtitle of this book, "The Practice of Medical Microbiology," aptly describes its design and function. The first part of the book discusses in 16 chapters the various technical methods employed in diagnostic laboratories devoted to microbiology, mycology and virology—including the diagnosis of rickettsial, chlamydial and mycoplasmal diseases. The second part of the book deals with the specifics of identifying the different types of microorganisms and carrying out serologic tests to support the clinician's diagnosis and therapy.

The series of distinguished British authors assures reliability, but also carries the implication that certain methods might not be the preferred ones in the United States, such as described in the second edition of the *Manual of Clinical Microbiology*, Lennette, Spalding and Truant, Eds., published by the American Society of Microbiology in 1974. There is much overlap and similarity between the two books. Both are directed primarily at the director, or principal technologist of the microbiology laboratory of a large hospital which also serves physicians in the community. Both books are of high standard and both can be recommended to those to whom they are addressed. Neither is likely to have significant appeal to a physician or medical student who is not principally concerned with the technical detail of microbiologic diagnosis.

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DISEASES OF BONES AND JOINTS—Second Edition—Louis Lichtenstein, MD, Clinical Professor of Pathology, University of California, San Francisco; Professor Extraordinario, National University of Mexico; Consultant in Pathology, Children's Hospital, San Francisco, and U.S. Naval Hospital, Oakland; Consultant in Orthopaedic Pathology, St. Joseph's Hospital and Mt. Zion Hospital and Medical Center, San Francisco. The C. V. Mosby Company, Publishers, 3301 Washington Boulevard, St. Louis, MO (63103), 1975. 314 pages with 332 illustrations, $27.50.

I have been personally acquainted with Dr. Louis Lichtenstein, having had an opportunity to know and work with him for several years when we were both associated, he in pathology and I in orthopedics, at the United States Veterans Hospital, West Los Angeles. His observations and interpretation of pathological conditions in bones thoroughly impressed me and others associated with him—not only in pathology but also in related clinical fields. I can therefore thoroughly attest to his ability and integrity in the field of bone and joint pathology. The first edition published in 1970 was a real contribution to the field of bone tumors.

In this second edition dealing with diseases of bone and joints, he has capably added to and elaborated on the contents of the first edition, and certainly deals more fully with subjects such as infections, the effects of pituitary growth hormone, hyperparathyroidism, the mucopolysaccharidoses (particularly gargoylism and its variants), the lipoidoses, sickle cell anemia, fluorosis, radiation osteitis, radiation induced neoplasms, intraosseous ganglia, degeneration and rupture of intervertebral discs, hypertrophic osteoarthropathy and pseudogout. There are a number of new illustrations in the second edition, both roentgenograms and photomicrographs; also a number of the legends have been amplified to enhance the usefulness of the illustrations.

The author, with his background and interests, necessarily emphasizes the actual pathology of these lesions throughout, but has made every effort without going too far afield to integrate basic pathological data with essential clinical information and with relevant observations in genetics, molecular biology, biochemistry and other fields, with a view to presenting a well-rounded comprehensive picture of skeletal disease. This excellent and outstanding second edition, in my opinion, can and will serve as a very fine reference book, not only for orthopedists but for general surgeons, radiologists, pathologists, pediatricians, internists and others in medicine, and those in allied sciences.

I thus without reservation can recommend this book as a comprehensive and a very worthwhile reference for those interested in the interpretation and diagnosis of the numerous conditions pertaining to diseases of bones and joints.

PAUL E. McMASTER, MD
Beverly Hills

in memoriam

Bramwell, Lavon, Yorba Linda. Died June 22, 1976 of heart disease, aged 77. Graduate of the University of California Medical School, Berkeley-San Francisco, 1930. Licensed in California in 1930. Dr. Bramwell was a member of the Orange County Medical Association.

Brown, William Wilfred, jr., Riverside. Died January 1, 1977 in Riverside, aged 60. Graduate of the University of Texas School of Medicine, Galveston, 1941. Licensed in California in 1965. Dr. Brown was a member of the Riverside County Medical Association.

Clarke, James Spencer, Sepulveda. Died May 19, 1976 of bronchogenic carcinoma, aged 57. Graduate of Harvard Medical School, Boston, 1943. Licensed in California in 1953. Dr. Clarke was a member of the Los Angeles County Medical Association.

Dagoberg, Albin W., Porterville. Died January 24, 1977, aged 79. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1932. Licensed in California in 1932. Dr. Dagoberg was a retired member of the Tulare County Medical Society.

Hackim, Albert S., San Diego. Died January 7, 1977 in San Diego, aged 63. Graduate of Wayne University College of Medicine, Detroit, 1943. Licensed in California in 1947. Dr. Hackim was a member of the San Diego County Medical Society.

Janda, Gurbachan Singh, Yuba City. Died January 4, 1977 in Fremont. aged 64. Graduate of Jefferson Medical College of Thomas Jefferson University, Philadelphia, 1934. Licensed in California in 1969. Dr. Janda was a member of the Yuba-Sutter-Colusa County Medical Society.

LaStovic, Joseph James, Santa Rosa. Died January 17, 1977 in Santa Rosa of malignant melanoma, aged 58. Graduate of the University of Alabama School of Medicine, Birmingham, 1961. Licensed in California in 1963. Dr. LaStovic was a member of the Sonoma County Medical Association.

Leggo, R. Christopher, Sacramento. Died January 27, 1977 in Sacramento of cerebrovascular accident, aged 80. Graduate of McGill University Faculty of Medicine, Montreal, 1919. Licensed in California in 1921. Dr. Leggo was a retired member of the Sacramento County Medical Association.

Lerned, Morris B., Laguna Hills. Died May 24, 1976 of cerebrovascular accident, aged 76. Graduate of Cornell University Medical College, New York, 1930. Licensed in California in 1933. Dr. Lerned was a retired member of the Los Angeles County Medical Association.

Marshall, Oscar Chauncey, Watsonville. Died January 21, 1977 in Watsonville of heart disease, aged 81. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1926. Licensed in California in 1926. Dr. Marshall was a member of the Santa Cruz County Medical Society.

Mouritsen, Holger S., Richmond. Died January 30, 1977 in San Pablo of myocardial infarction, aged 61. Graduate of Rush Medical College, Chicago, 1942. Licensed in California in 1943. Dr. Mouritsen was a retired member of the Alameda-Contra Costa Medical Association.

Myers, Paul White, Fresno. Died January 28, 1977 in Fresno, aged 53. Graduate of Indiana University School of Medicine, Bloomington-Indianapolis, 1945. Licensed in California in 1952. Dr. Myers was a member of the Fresno-Madera Medical Society.

Rice, Frank M., San Francisco. Died February 3, 1977 in San Francisco, aged 76. Graduate of Tufts College Medical School, Boston, 1924. Licensed in California in 1925. Dr. Rice was a retired member of the San Francisco Medical Society.

Stegeman, Wilson, Santa Rosa. Died January 1, 1977 in Santa Rosa of cancer, aged 79. Graduate of Rush Medical College, Chicago, 1925. Licensed in California in 1930. Dr. Stegeman was a retired member of the Sonoma County Medical Association.

Varden, Arthur E., San Bernardino. Died January 3, 1977 in San Bernardino, aged 74. Graduate of Washington University School of Medicine, St. Louis, 1929. Licensed in California in 1929. Dr. Varden was a retired member of the San Bernardino County Medical Society.

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(Continued on Page 20)

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(Continued from Page 19)

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CANCER

March 16-19—**Modern Concepts in Oncology—5th Annual Seminar.** UCLA at Beverly Hilton Hotel, Beverly Hills. Wednesday-Saturday.

March 19—**Cancer Screening and Cancer Control.** UCSF at Childrens Hospital, San Francisco. Saturday.

March 25—**Cancer of the Ovary.** California Hospital Medical Center, Los Angeles. Friday. Contact: Kenneth L. Senter, MD, Dir., Med. Ed., CHMC, 1414 S. Hope St., Los Angeles 90015. (213) 748-2411.

March 26—**Tumor Immunology, Clinical Applications.** San Francisco Regional Tumor Foundation at Fireman Fund Building, San Francisco. Saturday. Contact: Norma Schlager, PhD, S.F. Regional Tumor Foundation, 14th and Lake, San Francisco 94118. (415) 221-2132.

April 22-23—**Medical and Surgical Treatment of Gastrointestinal Cancer.** Scripps Clinic Medical Institutions, La Jolla. Friday-Saturday. $50. Contact: Williamson B. Strum, MD, Scripps Clinic Med. Institutions, 10666 N. Torrey Pines Rd., La Jolla 92037.

May 14-15—**Skin Cancer.** UCSF. Saturday-Sunday.

May 21-22—**Management of Cancer—3rd Annual Workshop.** Institute for Cancer and Blood Research and Century City Hospital Radiation Therapy Center at Riviera Country Club, Pacific Palisades. Saturday-Sunday. 16 hrs. Contact: Howard R. Bierman, MD, Sci. Dir., Institute for Cancer and Blood Research, 140 N. Robertson Blvd., Beverly Hills 90211. (213) 655-4706.

June 20-24—**Head and Neck Oncology.** UCLA. Monday-Friday.

MEDICINE

March 15-16—**American College of Physicians—Hawaii Regional Meeting.** Pacific Club, Honolulu. Tuesday-Wednesday. Contact: Bernard W. D. Fong, MD, 97 Dowsett Ave., Honolulu 96817.

March 17-19—**Cardiovascular Disease—1977: Practical Diagnosis and Management.** American College of Cardiology at Hotel del Coronado, Coronado. Thursday-Saturday. Contact: Mary Anne McInerny, Dir., Dept. of Cont. Ed. Prog., ACC, 9650 Rockville Pike, Bethesda, Md. 20014.

March 18—**Practical Approach to Coagulation.** PMC. Friday.

March 21-25—**Cardiac Electrophysiology.** USC at Erawan Garden Hotel, Palm Springs. Monday-Friday.

March 21-25—**Recent Advances in Endocrinology and Metabolism.** UCSF at Sheraton Palace, San Francisco. Monday-Friday.

March 21-April 1—**Intensive Review of Internal Medicine.** USC. Two weeks.

March 24-25—**Cardiac Disease for the Practicing Physician, Diagnosis and Management 1977—3rd Annual Symposium.** Los Angeles Heart Institute at St. Vincent Medical Center, Los Angeles. Thursday-Friday. 10 hrs. $100. Contact: Irma Larsen, RN, L.A. Heart Institute, 123 S. Alvarado St., Los Angeles 90057. (213) 413-5220.

March 28-April 1—**Consultant's Course in Dermatology.** UCSF. Monday-Friday.

March 30—**Cardiac Care in Your Office.** American Heart Assn., Central Valley Chapter, at Sheraton Inn, Fresno. Wednesday. 6½ hrs. $35. Contact: Norman Sharrer, MD, 3835 N. West Ave., Fresno 93705.

April 4-13—**Cardiology for the Consultant: A Clinician's Retreat.** American College of Cardiology at Rancho Santa Fe. 10 days. Contact: Mary Ann McInerny, Dir., Dept. of Cont. Ed. Programs, ACC, 9650 Rockville Pike, Bethesda, MD 20014.

April 6—**Current Concepts of Hemophilia and Related Disorders.** L.A. Society of Internal Medicine at L.A. Co. Med. Assn., Los Angeles. Wednesday. Contact: Jerry Koplowitz, MD, 5410 Wilshire Blvd., Los Angeles. (213) 937-5514.

April 6-May 25—**Current Practical Cardiology—1977.** Daniel

(Continued on Page 26)

KEY TO ABBREVIATIONS AND SYMBOLS

Medical Centers and CMA Contacts for Information

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103. (415) 777-2000.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Duane Dillman, PhD, Director, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 564-5911, ext. 391.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr., MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, Ext. 2400.

PMC: Pacific Medical Center
Contact: Allen J. Enelow, MD, Chairman, Education Committee, Pacific Medical Center, P.O. Box 7999, San Francisco 94120. (415) 563-4321.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Neil C. Andrews, MD, Chairman, Department of Postgraduate Medicine, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, California College of Medicine, Irvine
Contact: Robert Combs, MD, Associate Dean, Continuing Medical Education, University of California, Irvine—California College of Medicine, Irvine 92717 (714) 833-5991.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, P.O. Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: David Allan, MD, Associate Dean for Continuing Medical Education, 1309 Basic Sciences Building, University of California, San Diego, School of Medicine, La Jolla 92037. (714) 452-3708.

UCSF: University of California, San Francisco
Contact: Malcolm S. M. Watts, MD, Associate Dean and Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 226-2047.

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Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. As with all CNS-acting drugs, caution patients against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Though physical and psychological dependence have rarely been reported on recommended doses, use caution in administering Librium® (chlordiazepoxide hydrochloride) to known addiction-prone individuals or those who might increase dosage; withdrawal symptoms (including convulsions), following discontinuation of the drug and similar to those seen with barbiturates, have been reported.

***Usage in Pregnancy:* Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

As with all anticholinergic drugs, an inhibiting effect on lactation may occur.

Precautions: In elderly and debilitated, limit dosage to smallest effective amount to preclude development of ataxia, oversedation or confusion (not more than two capsules per day initially; increase gradually as needed and tolerated). Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider pharmacologic effects of agents, particularly potentiating drugs such as MAO inhibitors and phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions (*e.g.*, excitement, stimulation and acute rage) have been reported in psychiatric patients. Employ usual precautions in treatment of anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation have been reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship has not been established clinically.

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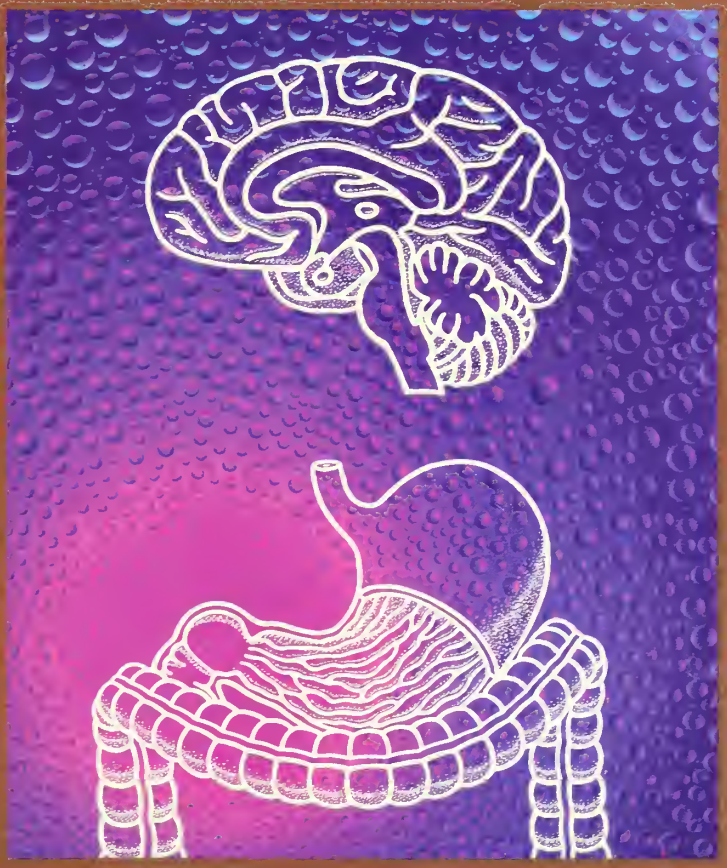

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ease see brief summary of prescribing information on preceding page.

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(Continued from Page 23)

Freeman Hospital, Inglewood. Wednesdays, 6:30-9:00 p.m. 16 hrs. $100. Contact: Donald Dennis, PhD, Dir. of Med. Ed., Daniel Freeman Hospital, 333 N. Prairie Ave., Inglewood 90301. (213) 674-7050, ext. 127.

April 16—**The Endocrine and Metabolic Aspects of Medical and Surgical Diseases—6th Annual Symposium.** South Coast Community Hospital, South Laguna. Saturday. 7 hrs. $40. Contact: Eugene B. Levin, MD, Dir. of Med. Ed., So. Coast Community Hosp., 31872 Coast Highway, So. Laguna 92677. (714) 499-1311.

April 16—**Gastroenterology.** Central San Joaquin Valley Area Health Education Center and Central Calif. Committee for Gastroenterology at Fresno Community Hospital, Fresno. Saturday. $35. Contact: Mr. Remi Barron, 5110 E. Clinton Way, Fresno 93728. (209) 252-2851.

April 18-22—**Advances in Internal Medicine.** UCSF. Monday-Friday.

April 23—**Controversies in Internal Medicine.** The San Jose Hospital and Health Center, Inc., and San Jose Hospital Foundation at Marriott's Great America, Santa Clara. Saturday. 6 hrs. $25. Contact: Stanley Skillicorn, MD, Dir. of Med. Ed., The San Jose Hosp. and Health Ctr., Inc., 675 E. Santa Clara, San Jose 95112. (408) 998-3212.

April 28-30—**New Approaches to Cardiac Diagnosis.** PMC at Fairmont Hotel, San Francisco. Thursday-Saturday.

May 6-7—**Update of Immunology and Allergy.** UCSD at Hilton Hotel, San Diego. Friday-Saturday.

May 7-14—**Diagnostic and Therapeutic Skills in Internal Medicine.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 30 hrs.

May 15-18—**American Thoracic Society—Annual Scientific Meeting.** Hilton Hotel, San Francisco. Sunday-Wednesday. Contact: Mr. S. R. Iannotta, Assoc. Ex. Dir., ATS, 1740 Broadway, New York 10019. (212) 245-8000.

May 20—**American Heart Association, California Affiliate—Scientific Sessions for Physicians.** Hyatt House, San Jose. Friday. Contact: Marilyn Probst, Admin. Asst., AHA, Calif. Affiliate, 1370 Mission St., San Francisco. (415) 626-0123.

May 20—**Stomatology.** STAN. Friday. 6 hrs.

May 20-21—**Hematology.** UCSF. Friday-Saturday.

May 21—**EKG Workshop.** PMC at Miyako Hotel, San Francisco. Saturday.

May 27-29—**New Concepts in Clinical Electrocardiography.** American College of Cardiology at Century Plaza Hotel, Los Angeles. Friday-Sunday. Contact: Mary Anne McInerny, Dir., Dept. of Cont. Ed. Prog., ACC, 9650 Rockville Pike, Bethesda, MD 20014.

June 1-July 27—**Review of ACP Medical Knowledge Self Assessment Test IV.** PMC. Wednesdays, 7-10 p.m.

June 4—**Pulmonary Artery Catheters and Ventilators.** PMC. Saturday.

June 6-October 18—**Intensive Review of Recent Advances in Internal Medicine—3rd Annual.** UCLA. Monday evenings.

June 7-10—**Echocardiography—Fundamentals and New Developments in Cardiac Ultrasound.** American College of Cardiology at Town and Country Hotel, San Diego. Tuesday-Friday. Contact: Mary Anne McInerny, Dir., Dept. of Cont. Ed. Prog., ACC, 9650 Rockville Pike, Bethesda, MD 20014.

June 9-11—**Concepts and Controversies in Cardiology—1977.** Hospital of the Good Samaritan and American Heart Assn. of Greater L.A. at Hospital of the Good Samaritan, Los Angeles. Thursday-Saturday. Contact: Janie Sternal, Coord., CME, Hosp. of the Good Samaritan, 616 S. Witmer, Los Angeles 90017. (213) 488-8123.

June 18—**Allergy for the Office Practice.** PMC. Saturday.

June 24-26—**Dermatomycology.** UCSF. Friday-Sunday.

July 1-3—**Arthritis Education Workshop.** STAN. Friday-Sunday.

OBSTETRICS AND GYNECOLOGY

March 18—**Birth Defects, Genetics and the High Risk Patient.** UCD at Sacramento Inn, Sacramento. Friday.

March 18—**Diabetes in Pregnancy.** USC. Friday.

March 18-19—**Obstetrics and Gynecology—22nd Annual Symposium.** Southern Calif. Permanente Medical Group at Bonaventure Hotel, Los Angeles. Friday-Saturday. Contact: Shirley Gach, So. Calif. Permanente Medical Group, 4900 Sunset Blvd., Room 6014, Los Angeles 90027. (213) 667-4241.

March 25-27—**Gynecological Urology.** USC at Marriott Hotel, Newport Beach. Friday-Sunday.

May 14—**Alternative Approaches to Childbirth.** UCLA. Saturday.

PEDIATRICS

March 25-26—**Aspects of Adolescent Medicine.** Ojai Valley Community Hospital; National Medical Enterprises, Inc.; Doctor's Hospital, Lakewood; Ventura Co. Academy of Family Physicians at Ojai Valley Inn and Country Club, Ojai. Friday-Saturday. 14 hrs. $20. Contact: E. William Jackson, MD, Ojai Community Hosp., 1306 Maricopa Highway, Ojai 93023. (805) 646-1401.

March 25-26—**Infectious Diseases in Children.** UCD at Sacramento Inn, Sacramento, Friday-Saturday.

March 27-31—**Radiological Approach to Pediatric Problems.** See Radiology, March 27-31.

April 4-6—**American Association of Pediatric Ophthalmology.** PMC at Holiday Inn, Union Square, San Francisco. Monday-Wednesday.

April 15-16—**Aches, Pain and Dramatic Diseases in Children and Young Adults.** USC at Children's Hospital, Los Angeles. Friday-Saturday.

May 2-6—**Pediatric Review.** USC. Monday-Friday.

May 5-7—**Care of the Sick Newborn.** Memorial Hospital Medical Center, Long Beach. Thursday-Saturday. Contact: Houchang D. Modanlou, MD, 2801 Atlantic Ave., Long Beach 90801.

May 12-14—**Advances in Pediatrics.** UCSF. Thursday-Saturday.

May 16-18—**Psychological Aspects of Juvenile Diabetes.** See Psychiatry, May 16-18.

May 30-June 1—**General Pediatrics—Annual Spring Meeting.** American Academy of Pediatrics, Northern Calif. Chapter 1, at Hyatt House, Monterey. Monday-Wednesday. 9 hrs. $100. Contact: Mrs. Helen Olson, Asst. Sec., AAP, No. Calif. Chapter 1, 2709 Calhoun St., Alameda 94501. (415) 522-8934.

June 17—**Conference on Prematurity—16th Annual.** STAN. Friday. Contact: Philip Sunshine, MD, Dept. of Pediatrics, Stanford Univ. Sch. of Med., Stanford 94305.

June 22-24—**Pediatric G.I. Course.** UCSF. Wednesday-Friday.

PSYCHIATRY

April 2—**Evaluation and Management of Dangerous Behavior.** UCD at Sacramento Host, Sacramento. Saturday.

May 15-18—**New Therapeutic Approaches with Biofeedback.** UCLA at Biltmore Hotel, Santa Barbara. Sunday-Wednesday.

May 16-18—**Psychological Aspects of Juvenile Diabetes.** Diabetic Youth Foundation and American Diabetes Assn. at Bear Skin Meadow Camp. Monday-Wednesday. Contact: Diabetic Youth Foundation, 1128 Irvin St., San Francisco 94122. (415) 731-5113.

May 19-22—**Clinical Hypnosis—Introductory and Advanced Course.** See Of Interest To All, May 19-22.

June 3-4—**Psychosocial Care of the Dying Patient.** UCSF. Friday-Saturday.

June 26-July 1—**Comparative Psychotherapies.** USC at Vacation Village, San Diego. One week.

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RADIOLOGY AND PATHOLOGY

March 17-19—**Annual Western-International CT Scanning Symposium.** Memorial Hospital Medical Center, Long Beach. Thursday-Saturday. 15 hrs. $200. Contact: Margaret Frederick, Center for Health Education, Memorial Hosp. Med. Ctr., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3823.

March 27-31—**Radiological Approach to Pediatric Problems.** USC at Bonaventure Hotel, Los Angeles. Sunday-Thursday.

April 29-30—**Sierra Valley Nuclear Medicine Association—Annual Symposium.** Sahara Tahoe Hotel, South Lake Tahoe. Friday-Saturday. Contact: Martha Frazer, Mercy San Juan Hospital, Dept. of Nuclear Medicine, 6501 Coyle Ave., Carmichael 95608.

May 14—**Radiological Evaluation of the Liver, Pancreas and Biliary Tract.** UCD at Woodlake Inn, Sacramento. Saturday.

June 3-5—**Spring Diagnostic Ultrasound Conference—2nd Annual.** Los Angeles Radiological Society at Century Plaza Hotel, Los Angeles. Friday-Sunday. Contact: Earl P. Detrick, MD, Westlake Community Hospital, 4415 Lakeview Canyon Rd., Westlake Village 91361.

June 18-25—**Lab Management for Pathologists.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week.

June 19-24—**Pathology of the Lung.** UCSD. Sunday-Friday.

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SURGERY AND ANESTHESIOLOGY

March 17-19—**Plastic Ophthalmic Surgery: Intraocular Lenses Insertion.** St. Mary's Hospital and Medical Center, San Francisco. Thursday-Saturday. 24 hrs. $250. Contact: J. A. Sarrail, MD, 450 Sutter St, San Francisco. (415) 397-1500.

March 25-26—**Retina Workshop.** Retina Research Fund of St. Mary's Hospital and Medical Center at Hyatt on Union Square, San Francisco. Friday-Saturday. 12 hrs. $135. Contact: Ms. Claire Ohiyon, c/o Howard Schatz, MD, 3637 Sacramento St., San Francisco 94118. (415) 921-4860.

March 25-27—**Gynecological Urology.** See Obstetrics and Gynecology, March 25-27.

March 28-31—**American College of Surgeons—5th Annual Spring Meeting.** Bonaventure Hotel, Los Angeles. Monday-Thursday. Contact: Edwin W. Gerrish, MD, Asst. Dir., Assembly, ACS, 55 E. Erie St., Chicago 60611. (312) 664-4050.

March 31-April 1—**Diseases of the Urinary Tract.** STAN at Rickey's Hyatt House, Palo Alto. Thursday-Friday. 16 hrs. $150.

April 1-3—**Management of Trauma.** UCSD at Sheraton Harbor Island Hotel, San Diego. Friday-Sunday. $175. Contact: Nomi Feldman, Box 705, La Jolla 92038.

April 4-6—**American Association of Pediatric Ophthalmology.** See Pediatrics, April 4-6.

April 7-9—**Plastic and Reconstructive Surgery of the Eyelids and Orbits.** UCLA. Thursday-Saturday.

April 14-15—**Office Orthopedics.** See Of Interest To All, April 14-15.

April 15-16—**Hand Injuries and Infections.** PMC. Friday-Saturday.

April 16—**The Endocrine and Metabolic Aspects of Medical and Surgical Diseases.** See Medicine, April 16.

April 21-22—**Diagnosis and Clinical Management of Glaucoma.** Jules Stein Eye Institute at Century Plaza Hotel, Los Angeles. Thursday-Friday. Contact: Jules Stein Eye Institute, UCLA School of Medicine, Los Angeles 90024.

April 21-22—**Phaco-Fragmentation.** UCSF. Thursday-Friday.

April 21-23—**General Surgery—Annual Course.** Thursday-Saturday.

April 23—**Audiology for Practicing Physicians.** PMC. Saturday.

April 28-29—**Current Problems in Intensive Care: Mechanical Ventilation.** UCSF at Stanford Court Hotel, San Francisco. Thursday-Friday. $125.

April 28-30—**Retina Workshop.** Retina Research Fund of St. Mary's Hospital and Medical Center, San Francisco, at Silverado, Napa Valley. Thursday-Saturday. 12 hrs. $135.

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Robert Hodges, MD, Professor and Chief, Nutrition Division, Department of Internal Medicine, University of California, Davis, California

Leonard L. Madison, MD, Professor of Medicine, Southwestern Medical School, University of Texas Health Science Center, Dallas, Texas

Arthur Robinson, PhD, President, Director, Research Professor, Linus Pauling Institute of Science & Medicine, Menlo Park, California

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John Schroeder, MD, Associate Professor of Medicine, Stanford University School of Medicine

Charles R. Shuman, MD, Professor of Medicine, Temple University School of Medicine, Chief, Section of Metabolism, Philadelphia, Pennsylvania

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For information, write Health Sciences, UCLA Extension, 10995 Le Conte Ave., Los Angeles, CA 90024, or call Marilyn Murray at (213) 825-7186.

Contact: Ms. Claire Ohiyon, c/o Howard Schatz, MD, 3637 Sacramento St., San Francisco 94118. (415) 921-4860.

April 30—**Flexible Bronchofibroscopy.** PMC. Saturday.

April 30-May 7—**Management of the Surgical Patient.** STAN at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week $275.

May 1—**Clarence E. Stafford Memorial Surgical Symposium and Lecture—2nd Annual.** White Memorial Medical Center, Dept. of General Surgery; and LLU at Hilton Hotel, Los Angeles. Sunday. 8 hrs. $40. Contact: Dept. of Gen. Surgery, White Mem. Med. Ctr., 1720 Brooklyn Ave., Los Angeles 90033. (213) 263-6100 or (213) 269-9131, ext. 429.

May 15-19—**Fifteenth Biennial Western Conference on Anesthesiology.** Hyatt Regency Hotel, San Francisco. Sunday-Thursday. 18 hrs. $100. Contact: Exec. Sec., BWCA, 707-2525 Willow St., Vancouver, B.C., Canada V5Z 3N8.

May 19-20—**Phaco-Fragmentation.** UCSF. Thursday-Friday.

May 19-21—**Neurosurgery—7th Annual Course.** UCSF at Hyatt on Union Square, San Francisco. Thursday-Saturday.

May 20-21—**Anesthesiology Refresher Course.** Biennial Western Conference on Anesthesiology at Del Monte Hyatt House, Monterey. Friday-Saturday. 8¼ hrs. $50. Contact: Exec. Sec., BWCA, 707-2525 Willow St., Vancouver, B.C., Canada V5Z 3N8.

May 26-28—**Retina Workshop.** Retina Research Fund of St. Mary's Hospital and Medical Center, San Francisco, at Quail Lodge, Carmel Valley. Thursday-Saturday. 12 hrs. $135. Contact: Ms. Claire Ohiyon, c/o Howard Schatz, MD, 3637 Sacramento St., San Francisco 94118. (415) 921-4860.

June 3-4—**Ophthalmology Update II.** PMC. Friday-Saturday.

June 9-10—**Trauma.** UCSF at Mary's Help Hospital, Daly City. Thursday-Friday.

June 9-11—**Surgical Nutrition.** UCSF at Hilton Hotel, San Francisco. Thursday-Saturday.

June 9-12—**California Society of Anesthesiologists—Annual Scientific Meeting.** Town and Country Hotel, San Diego. Thursday-Sunday. Contact: CSA, 100 S. Ellsworth Ave., Suite 806, San Mateo 94401.

June 10-12—**Modern Laryngoscopy and Bronchoesophagoscopy: A Theoretical and Practical Course.** UCLA. Friday-Sunday. Contact: Paul H. Ward, MD, Div. of Head and Neck Surgery, UCLA Sch. of Med., Los Angeles 90024.

June 16-18—**Highlights of Ophthalmology.** PMC. Thursday-Saturday.

June 18-19—**American Association for Study of Headache.** See Of Interest To All, June 18-19.

July 2-9—**Manipulation, Mobilization and Related Techniques in Treatment of Musculo-Skeletal and Myofascial Pain Syndromes.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. $275.

Orthopaedic Audio-Synopsis Foundation. A non-profit service for Orthopaedic Surgeons publishing monthly recorded teaching programs which include summaries of pertinent literature and excerpts from national and international orthopaedic meetings. Monthly c-60 cassette tapes. Annual subscription rate $75 ($37.50 for residents). Contact: A. Harris, Man. Ed., OASF, 1510 Oxley St., So. Pasadena 91030. (213) 682-1760.

OF INTEREST TO ALL PHYSICIANS

March 16-April 16—**Family Medicine Tutorial.** DREW. Wednesday mornings.

March 18-24—**LLU School of Medicine—Annual Postgraduate Convention.** Friday-Thursday. Contact: Alumni Association, LLU.

March 21-25—**Postgraduate Institute for Emergency Physicians, Symposium II.** UCSD. Monday-Friday.

March 26—**Prevention of Sports Injuries.** Sonoma County Medical Assn., Community Hosp. of Sonoma County and Sonoma State College at Sonoma State College, Rohnert Park. Saturday. Contact: William E. Tewksbury, Asst. Exec. Dir., SCMA, 3452 Mendocino Ave., Santa Rosa 95401. (707) 544-2010.

March 26-27—**Practical Endocrinology for the Primary Care Physician.** UCLA. Saturday-Sunday. 12 hrs. $125.

March 28-April 1—**Therapy: Principles and Use of Drugs.** STAN. Monday-Friday.

April 1-2—**Providence Hospital—Annual Spring Seminar.** Providence Hospital, Oakland. Friday-Saturday. 9 hrs. Contact: Nancy Hansen, Coord., Med. Staff, Providence Hospital, Box 23020, Oakland 94623. (415) 835-4500, ext 373.

April 1-2—**West Coast Counties Postgraduate Institute.** CMA at Quail Lodge, Carmel. Friday-Saturday.

April 2—**Total Parenteral Nutrition.** PMC. Saturday.

April 13-14—**American Geriatrics Society—34th Annual Meeting.** Fairmont Hotel, San Francisco. Wednesday-Thursday. Contact: Marcia Roye, Assoc. Exec. Dir., AGS, 10 Columbus Cir., New York 10019. (212) 582-1333.

April 14-15—**Office Orthopedics.** USC. Thursday-Friday.

April 15-16—**Aches, Pain and Dramatic Diseases in Children and Young Adults.** See Pediatrics, April 15-16.

April 15-16—**Practical ENT for Primary Physicians.** UCSF. Friday-Saturday.

April 16-23—**Emergency Medicine.** USC at Kona Surf Hotel, Kona, Hawaii. One week.

April 18-October 25—**Intensive Review of Family Practice.** USC. Thursday evenings.

April 20-June 29—**An Exploration of Traditional Chinese Health Care Practices.** UCLA. Wednesday evenings.

April 23—**Audiology for Practicing Physicians.** See Surgery, April 23.

April 28-29—**Current Problems in Intensive Care.** UCSF at Stanford Court, San Francisco. Thursday-Friday.

April 29—**Continuing Medical Education Seminar—6th Annual.** LLU at Bakersfield. Friday.

April 29-30—**San Joaquin Valley Counties Postgraduate Institute.** CMA at Ahwahnee Hotel, Yosemite. Friday-Saturday.

May 6-8—**Family Medicine Intensive Review.** DREW. Friday-Sunday.

May 7—**8th Annual Symposium on Clinical Pharmacology.** STAN at Palo Alto Medical Clinic, Palo Alto. Saturday. Contact: Stanley Cohen, MD, Clinical Pharm., Dept. of Medicine, Stanford Univ. Sch. of Med., Stanford 94305. (415) 497-5315.

May 7-8—**Summer Emergencies.** Dept. of Emergency Medicine, Valley Medical Center, Fresno; San Joaquin Valley Area Health Education Center at Holiday Inn, Monterey. Saturday-Sunday. $80, physicians; $40, residents, students,

nurses. Contact: Frank Mannix, MD, Dept. of Emergency Med., Valley Med. Ctr., 445 S. Cedar, Fresno 93702.

May 9-13—**Topics in Emergency Medicine.** UCSF at Franklin Hospital, San Francisco. Monday-Friday.

May 16-20—**Postgraduate Institute for Emergency Physicians, Symposium I.** UCSD at Sheraton Harbor Island Hotel, San Diego. Monday-Friday.

May 16-22—**Diving Medicine.** UCSF at VA Hospital, Fresno. Monday-Sunday.

May 19-21—**Ambulatory Monitoring.** Medical Communications and Services Assn., STAN and Stanford Research Institute at Fairmont Hotel, San Francisco. Thursday-Saturday. 14 hrs. $100. Contact: Nancy Jacobsen, MCSA, 1107 N.E. 45th St., Rm. 315, Seattle, WA 98105. (206) 633-0505.

May 19-22—**Clinical Hypnosis—Introductory and Advanced Course.** American Society of Clinical Hypnosis at San Francisco. Thursday-Sunday. 25 hrs. $225. Contact: William F. Hoffman, Jr., Exec. Sec., ASCH, Education and Research Foundation, 2400 E Devon Ave., Suite 218, Des Plaines, ILL 60018. (312) 297-3317.

May 21-22—**Family Practice Management of Ischemic Heart Disease.** UCLA. Saturday-Sunday.

May 22-27—**Fingers-to-the-Toes—An Orthopedic Approach for the General Practitioner.** UCD at Stanford Sierra Camp, Fallen Leaf Lake. Sunday-Friday.

May 25-27—**Pain: Diagnosis and Management.** UCLA. Wednesday-Friday.

May 26-30—**Patient Oriented Applied Medical Advances.** UCSF at Hawaii. Thursday-Monday.

June 3-4—**Psychosocial Care of the Dying Patient.** See Psychiatry, June 3-4.

June 8-12—**California Chapter, American College of Emergency Physicians—Scientific Assembly.** Fairmont Hotel, San Francisco. Wednesday-Sunday. Contact: Calif. Chapter, ACEP, 58 California Ave., Orinda 94563.

June 9-11—**Management of Medical Problems.** PMC. Thursday-Saturday.

June 16-17—**Sports Medicine.** USC. Thursday-Friday.

June 18-19—**American Association for Study of Headache—Annual Meeting.** Hyatt on Union Square, San Francisco. Saturday-Sunday. Contact: Seymour Diamond, MD, Exec. Sec., Am. Assn. for Study of Headache, 5252 N. Western Ave., Chicago 60625. (312) 878-5558.

June 18-22—**American Medical Association—126th Annual Convention.** Fairmont Hotel, San Francisco. Saturday-Wednesday. Contact: AMA, 535 N. Dearborn St., Chicago 60610.

June 20-24—**Postgraduate Institute for Emergency Physicians, Symposium IV.** UCSD at Islandia Hotel, San Diego. Monday-Friday.

July 11-15—**Postgraduate Institute for Emergency Physicians, Symposium III.** UCSD at Hilton Hotel, San Diego. Monday-Friday.

July 31-August 5—**National Medical Association—82nd Annual Scientific Assembly.** Bonaventure Hotel, Los Angeles. Sunday-Friday. Contact: Alfred F. Fisher, Exec. Dir., NMA, 1625 Eye St., NW, Suite 725A, Washington, D.C. 20006.

Audio-Digest Foundation. A non-profit subsidiary of CMA. Twice-a-month tape recorded summaries of leading national meetings and surveys of current literature. Services by subscription in: Family Practice, Surgery, Internal Medicine, Ob/Gyn, Pediatrics, Psychiatry, Anesthesiology, Ophthalmology, Otorhinolaryngology. Catalog of lectures and panel discussions in all areas of medical practice also available. $90 per year. Also available are ACOG Audio Education Courses, edited and produced by Audio-Digest Foundation —32, 6- and 3-hour cassette courses available including: Family Life and Sexual Counseling; Medical Complications of Pregnancy; Gynecological Endocrinology; Psychosomatic Ob/Gyn; Immunology in Ob/Gyn; and Pediatric and Adolescent Gyn. Available soon: Cassette albums of State of the Art Lectures and Workshops from 1976 American College of Physicians meeting and Postgraduate Courses from 1976 American Psychiatric Association meeting. Contact: Mr. Claron L. Oakley, Editor, Suite 700, 1930 Wilshire Blvd., Los Angeles 90057. (213) 483-3451.

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Moderator:
WILLIAM A. ALTEMEIER, MD
Professor and Chairman, Department of Surgery
University of Cincinnati College of Medicine
Cincinnati, Ohio

Afternoon Program

II. Pulmonary Complications in the Surgical Patient

Moderator:
JOHN E. HODGKIN, MD
Assistant Professor of Medicine
Chief, Section of Medical Chest Diseases
Loma Linda University School of Medicine
Loma Linda, California

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training, practical aspects of clinical care and management. 160 hrs. Contact: John E. Peterson, MD, LLU.

Training of Physicians in Modern Concepts of Pulmonary Care. LLU. Four weeks or more, by arrangement. Diagnostic and therapeutic methods in medical chest disease, physiological methodology of modern pulmonary care programs, use of new instrumentation in the field. 160 hrs. Contact: John E. Hodgkin, MD, Chief, Section of Medical Chest Diseases, LLU.

Physician-in-Residence Preceptorship in Pulmonary Disease. USC, Pulmonary Disease Section, Dept. of Medicine and Postgraduate Medical Education. One month or more, by arrangement. Opportunity for practicing physician to achieve specified knowledge and skills in adult pulmonary medicine. Contact: Oscar J. Balchum, MD, PhD, USC.

Training for Physicians in Nephrology. LLU. Four weeks or more, by arrangement. Hemodialysis, peritoneal dialysis, renal biopsy, and kidney transplantation. 160 hrs. Contact: Robert E. Soderblom, MD, LLU.

Preceptorships in Cardiology. PMC. By arrangement. $200 per mo.; $500 for 3 mos. Contact: Arthur Selzer, MD, PMC.

Preceptorships in Practical Office Dermatology. PMC. Wednesdays or Fridays, 9:00 a.m.-12:00 noon, for 10 weeks. Periods begin Oct., Jan., or April. $100. Contact: Harold M. Schneidman, MD, Dept. of Dermatology, PMC.

Preceptorships in Infectious Disease. PMC. Full time for four weeks. To be arranged. $250. Contact: Rodney J. Valentine, MD, Chief, Div. of Infectious Diseases, PMC.

Preceptorships in Basic Sciences, Biochemistry and Biophysics, Dermatology, Echocardiography, International Health, Microbiology, Neurological Surgery, Obstetrics and Gynecology, Pediatrics, Pharmacology and Experimental Therapeutics, Physiology, Psychiatry, Urology. UCSF. By special arrangement.

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OREGON

COUNCIL ON MEDICAL EDUCATION

THIS BULLETIN of information regarding continuing education programs and meetings of various medical organizations in Oregon is supplied by the Council on Medical Education of the Oregon Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Council on Medical Education, Oregon Medical Association, 5210 SW Corbett Ave., Portland, OR 97201; or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

University of Oregon Medical School, Department of Internal Medicine, 3181 SW Sam Jackson Park Road, Portland 97201:

Every Tuesday, 8:00 a.m. to 9:00 a.m.—**Internal Medicine Grand Rounds.** Library Auditorium, University of Oregon Health Sciences Center, Portland. Contact: Stephen R. Jones, MD, Department of Internal Medicine, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, 97201.

Providence Medical Center, 700 NE 47th Avenue, Portland 97213:

Every Wednesday, 8:00 a.m. in the auditorium—**Spring Medical Grand Rounds,** Providence Medical Center. Contact: David N. Gilbert, MD, Director of Medical Education, Providence Medical Center, 700 NE 47th, Portland 97213.

University of Oregon Medical School, Infectious Disease Conferences. 3181 SW Sam Jackson Park Road, Portland.

Every Thursday, 12:00 Noon—**Infectious Disease Conference** (through June 2), Room 8B-60 UHS (University Hospital South).

FAMILY PRACTICE

Every Wednesday, 11:00 a.m. to 12:00 Noon. **Family Practice Grand Rounds.** Family Practice Center, University of Oregon Health Sciences Center. Contact: William A. Fisher, MD, University of Oregon Health Sciences Center, Department of Family Practice, 3181 SW Sam Jackson Park Road, Portland 97201.

May 5-8—**Oregon Academy of Family Physicians 30th Annual Scientific Assembly.** Salishan Lodge, Gleneden Beach. Contact: Skippie Patterson, Executive Secretary, Oregon Academy of Family Physicians, 2188 SW Main, Portland 97205.

INTERNAL MEDICINE

Every Tuesday, 8:00 a.m. to 9:00 a.m.—**Internal Medicine Grand Rounds.** Library Auditorium, University of Oregon Health Sciences Center, Portland. Contact: Stephen Jones, MD, Department of Internal Medicine, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland 97201.

SURGERY

March 15—**Portland Surgical Society.** Congress Hotel, Portland. Contact: William C. Awe, MD, 2222 NW Lovejoy, Portland 97210.

OF INTEREST TO ALL PHYSICIANS

March 15—**Drugs Prescribed for Heart Attack Patients.** Rogue Valley Memorial Hospital, Classroom Auditorium, Medford. Contact: Oregon Heart Association, 1500 SW 12th Avenue, Portland 97201.

March 15—**Multiple Myeloma.** Jantzen Beach Thunderbird, Portland. Contact: David N. Gilbert, MD, Providence Medical Center, 700 NE 47th, Portland 97213.

April 13-15—**University of Oregon Health Sciences Center Annual Alumni Meeting and Sommer Memorial Lectures.** Library Auditorium, University of Oregon Health Sciences Center. Contact: Michele Wiley, Medical Relations Officer, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland 97201.

April 20—**Biofeedback in Medicine.** Withycombe Hall, Oregon State University, Corvallis. Contact: R. L. Phillips, Ads A 600 Oregon State University, Corvallis 97331.

WASHINGTON, ALASKA, MONTANA AND IDAHO

In order to have future activities listed here or to receive information on these and other activities, please write Ms. Joan M. Kelday, Information Specialist, Continuing Medical Education, WAMI Program, University of Washington School of Medicine, Health Sciences Building, SC-64, Seattle, Washington 98195. Phone: (206) 543-6995.

March 16—**Surgery: Shock and Clinical Fluid Balance.** Wednesday. Univ. of Wash. in Billings, Mont. 1-3:30 p.m., Marillac Hall. 2½ hrs. Contact: Mrs. Frances Burt, Cont. Med. Ed., Marillac Hall, Billings, MT 59101. (406) 252-2121, Ext. 258.

March 16—**Metabolic Disorders in Pediatrics.** Wednesday. Univ. of Wash. in Ancortes, Wash. 7:30-10 a.m., Island Hospital, 2½ hrs. Contact: Harry Eiesland, MD, 24th and M Ave., Ancortes, WA 98221. (206) 292-3101.

March 17-18—**What's New in Internal Medicine.** Thursday-Friday. St. Joseph Hospital, Tacoma, Wash. 12 hrs. Contact: Mrs. Maxine Bailey, College of Medical Education, The University of Puget Sound, 1500 N. Warner, Tacoma, WA 98416. (206) 756-3152.

March 18-19—**Electromyography.** Friday-Saturday. Seattle. Contact: Pat Lind, Div. of CME, HSB SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-9495 or 543-1050.

March 18-19—**Otolaryngologic and Head and Neck Emergencies.** Friday-Saturday. Virginia Mason Medical Center Auditorium, Seattle. Hours and fee to be determined. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) 223-6898.

March 21-25—**Advances in Family Practice.** Monday-Friday. Health Sciences Bldg., Seattle. Contact: Pat Lind, Div. of CME, HSB SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-9495 or 543-1050.

March 24—**Internal Medicine Review: Lower Intestinal Diseases.** Thursday. Univ. of Wash. in Billings, Mont. 7-9:30 a.m., Marillac Hall. 2½ hrs. Contact: Mrs. Frances Burt,

Cont. Med. Ed., Marillac Hall, Billings, MT 59101. (406) 252-2121, Ext. 258.

March 25—**Internal Medicine Review: Lower Intestinal Diseases.** Friday. Univ. of Wash. in Missoula, Mont. 8:30-11 a.m., St. Patrick Hospital, 2½ hrs. Contact: James E. Gouaux, MD, 515 Kensington, Missoula, MT 59801. (406) 549-4581.

March 26—**Day of Pediatrics.** Saturday. Mary Bridge Children's Hospital, Tacoma, Wash. 6 hrs. Contact: Mrs. Maxine Bailey, College of Medical Education, The University of Puget Sound, 1500 N. Warner, Tacoma, WA 98416. (206) 756-3152.

March 28—**Internal Medicine Review: Immunologic Renal Disease.** Monday. Univ. of Wash. in Wenatchee, Wash. 7-9 p.m., Wenatchee Valley Clinic. 2 hrs. Contact: William M. McKee, MD, PO Box 489, Wenatchee, WA 98801. (509) 663-8711.

March 29—**Internal Medicine Review: Immunologic Renal Disease.** Tuesday. Univ. of Wash. in Yakima, Wash. 5-7 p.m., Memorial Hospital. 2 hrs. Contact: Harry Kimball, MD, Yakima Medical Center, Yakima, WA 98902. (509) 248-6791.

March 30-April 1—**30th National Conference on Rural Health.** Wednesday-Thursday. Washington Plaza Hotel, Seattle. Contact: Department of Rural and Community Health, AMA, 535 N. Dearborn St., Chicago, IL 60610.

April 1-2—**Oral-Facial Pain.** Friday-Saturday. Seattle. Contact: Pat Lind, Div. of CME, HSB SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-9495 or 543-1050.

April 6, 13, 20—**Tacoma General Topics.** Wednesdays. Tacoma General Hospital, Tacoma, Wash. 7:30-9:30 a.m. 6 hrs. Contact: Mrs. Maxine Bailey, College of Medical Education, The University of Puget Sound, 1500 N. Warner, Tacoma, WA 98416. (206) 756-3152.

April 14-15—**Respiratory Care.** Thursday-Friday. Seattle. Contact: Pat Lind, Div. of CME, HSB SC-50, Univ. of Wash. Sch. of Med., Seattle, WA 98195. (206) 543-9495 or 543-1050.

April 14-17—**Society for Obstetric Anesthesias and Perinatology.** Thursday-Saturday. Edgewater Inn, Seattle. Contact: D. H. Ralston, MD, Department of Anesthesiology, RN-10, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-4172.

April 15-16—**Nutrition for Physicians.** Friday-Saturday. Seattle. Contact: Pat Lind, Div. of CME, HSB SC-50, Univ. of Wash. Sch. of Med., Seattle, WA 98195. (206) 543-9495 or 543-1050.

April 19—**Surgery: Cancer and Trauma of the Head and Neck.** Tuesday. Univ. of Wash. in Missoula, Mont. 7-9 p.m., Community Hospital. 2 hrs. Contact: Mrs. Janet Perrin, 500 West Pine, Missoula, MT 59801. (406) 549-3782.

April 20—**Surgery: Cancer and Trauma of the Head and Neck.** Wednesday. Univ. of Wash. in Billings, Mont. 1-3:30 p.m., Marillac Hall. 2½ hrs. Contact: Mrs. Frances Burt, Cont. Med. Ed. Marillac Hall, Billings, MT 59101. (406) 252-2121, Ext. 258.

April 25—**Internal Medicine Review: Upper Intestinal Diseases —Esophagus to Ileum.** Monday. Univ. of Wash. in Wenatchee, Wash. 7-9 p.m., Wenatchee Valley Clinic. 2 hrs. Contact: William M. McKee, MD, P.O. Box 489, Wenatchee, WA 98801. (509) 663-8711.

April 26—**Internal Medicine Review: Upper Intestinal Diseases —Esophagus to Ileum.** Tuesday. Univ. of Wash. in Yakima, Wash. 5-7 p.m., Memorial Hosiptal. 2 hrs. Contact: Harry Kimball, MD, Yakima Medical Center, Yakima, WA 98902. (509) 248-6791.

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April 29-30—**Medical Alcoholism.** Friday-Saturday. Seattle. Contact: Pat Lind, Div. of CME, HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle, WA 98195. (206) 543-9495.

May 6-7—**Dermatology.** Friday-Saturday. Seattle. Contact: Pat Lind, Div. of CME, HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle, WA 98195. (206) 543-9495.

May 6-7—**High-risk Mother and Infant.** Friday-Saturday. Seattle. Contact: Pat Lind, Div. of CME, HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle, WA 98195. (206) 543-9495.

May 13-14—**Management of Acute Problems in Perioperative Care of the Surgical Patient.** Friday-Saturday. Virginia Mason Medical Center Auditorium, Seattle. Hours to be determined. $75. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) 223-6898.

May 18—**Evaluation of Acute Trauma.** Wednesday. Univ. of Wash. in Anacortes, Wash. 7:30-10 a.m., Island Hospital. 2½ hrs. Contact: Harry Eiesland, MD, 24th and M Ave., Anacortes, WA 98221. (206) 292-3101.

May 19-20—**Fluid Electrolyte Disorders: A Clinical Approach.** Thursday-Friday. Virginia Mason Medical Center Auditorium, Seattle. Hours and fee to be determined. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) 223-6898.

May 20-21—**Coronary Bypass Surgery.** Friday-Saturday. Seattle. Contact: Pat Lind, Div. of CME, HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle, WA 98195. (206) 543-9495.

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*In a new study 8 out of 10 patients with acute lower urinary tract infection, primarily cystitis, achieved sterile urine. All infections were nonobstructed. Susceptible organisms included *E. coli*, *Klebsiella-Aerobacter*, *Proteus mirabilis* and *Proteus vulgaris*.

No. of patients	Sterile urine	Clear culture <1000 organisms/ ml urine	Clear culture <10,000 organisms/ ml urine
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Basic therapy with convenience and economy in acute nonobstructed cystitis†

†due to susceptible organisms

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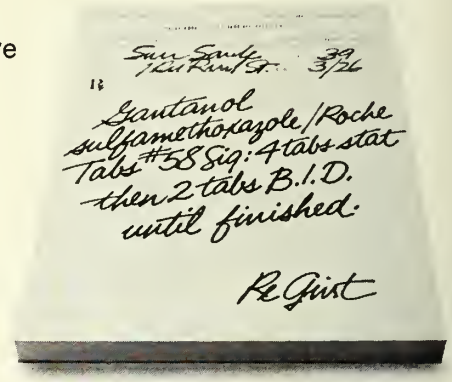
Basic therapy with convenience and economy in acute nonobstructed cystitis*

4 tablets (0.5 Gm each) STAT—then 2 tablets B.I.D. for 10-14 days

- ☐ Effective in nonobstructed cystitis.
- ☐ Active against susceptible strains of gram-negative and gram-positive organisms: *E. coli, Klebsiella-Aerobacter, Staph. aureus, Proteus mirabilis* and, less frequently, *Proteus vulgaris.*
- ☐ Rapid antibacterial blood and urine levels—in from 2 to 3 hours.
- ☐ Convenient, economical B.I.D. dosage.
- ☐ Contraindicated during pregnancy and the nursing period and in infants under 2 months of age.
- ☐ As with all sulfonamides, adequate fluid intake should be maintained during therapy; perform frequent CBC's and urinalyses with careful microscopic examination.



*due to susceptible organisms

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Acute, recurrent or chronic nonobstructed urinary tract infections (primarily nonobstructed pyelonephritis, pyelitis and cystitis) due to susceptible organisms, usually *E. coli, Klebsiella-Aerobacter, Staphylococcus aureus, Proteus mirabilis* and, less frequently, *Proteus vulgaris.* **Note: Carefully coordinate *in vitro* sulfonamide sensitivity tests with bacteriologic and clinical response; add aminobenzoic acid to follow-up culture media. The increasing frequency of resistant organisms limits the usefulness of antibacterials including sulfonamides, especially in chronic or recurrent urinary tract infections.** Measure sulfonamide blood levels as variations may occur; 20 mg/100 ml should be maximum total level.

Contraindications: Sulfonamide hypersensitivity; pregnancy at term and during nursing period; infants less than two months of age.

Warnings: Safety during pregnancy has not been established. Sulfonamides should not be used for group A beta-hemolytic streptococcal infections and will not eradicate or prevent sequelae (rheumatic fever, glomerulonephritis) of such infections. Deaths from hypersensitivity reactions, agranulocytosis, aplastic anemia and other blood dyscrasias have been reported and early clinical signs (sore throat, fever, pallor, purpura or jaundice) may indicate serious blood disorders. Frequent CBC and urinalysis with microscopic examination are recommended during sulfonamide therapy. Insufficient data on children under six with chronic renal disease.

Precautions: Use cautiously in patients with impaired renal or hepatic function, severe allergy, bronchial asthma; in glucose-6-phosphate dehydrogenase-deficient individuals in whom dose-related hemolysis may occur. Maintain adequate fluid intake to prevent crystalluria and stone formation.

Adverse Reactions: *Blood dyscrasias* (agranulocytosis, aplastic anemia, thrombocytopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia); *allergic reactions* (erythema multiforme, skin eruptions, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis); *gastrointestinal reactions* (nausea, emesis, abdominal pains, hepatitis, diarrhea, anorexia, pancreatitis and stomatitis); *CNS reactions* (headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo and insomnia); *miscellaneous reactions* (drug fever, chills, toxic nephrosis with oliguria and anuria, periarteritis nodosa and L.E. phenomenon). Due to certain chemical similarities with some goitrogens, diuretics (acetazolamide, thiazides) and oral hypoglycemic agents, sulfonamides have caused rare instances of goiter production, diuresis and hypoglycemia as well as thyroid malignancies in rats following long-term administration. Cross-sensitivity with these agents may exist.

Dosage: Systemic sulfonamides are contraindicated in infants under 2 months of age (except adjunctively with pyrimethamine in congenital toxoplasmosis).

Usual adult dosage: 2 Gm (4 tabs or teasp.) initially, then 1 Gm *b.i.d.* or *t.i.d.* depending on severity of infection.

Usual child's dosage: 0.5 Gm (1 tab or teasp.)/20 lbs of body weight initially, then 0.25 Gm/20 lbs *b.i.d.* Maximum dose should not exceed 75 mg/kg/24 hrs.

Supplied: Tablets, 0.5 Gm sulfamethoxazole; Suspension, 0.5 Gm sulfamethoxazole/teaspoonful.

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WARNING
This fixed combination drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual patient. If the fixed combination represents the dosage so determined, its use may be more convenient in patient management. The treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Indications: When the fixed combination represents the dosage determined by titration: Adjunctive therapy in edema associated with congestive heart failure, hepatic cirrhosis, the nephrotic syndrome. Corticosteroid and estrogen-induced edema, idiopathic edema; hypertension, when the potassium-sparing action of its 'Dyrenium' component is warranted.

Contraindications: Further use in progressive renal or hepatic dysfunction; hyperkalemia. Preexisting elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs. Routine use of diuretics in otherwise healthy pregnancy.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in severely ill patients with urine volume less than one liter/day, the elderly or diabetics, with suspected or confirmed renal insufficiency. Periodic determinations of serum K^+ should be made. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **The presence of a widened QRS complex or arrhythmia in association with hyperkalemia requires prompt additional therapy.** Thiazides are reported to cross the placental barrier and appear in breast milk; fetal or neonatal hyperbilirubinemia, thrombocytopenia, altered carbohydrate metabolism and other adverse reactions that have occurred in the adult may result. When used in pregnancy or in women who might bear children, weigh potential benefits against possible hazards to fetus. Adequate information on use in children is not available.

Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics, or those with suspected or confirmed renal insufficiency. Watch for signs of impending coma in severe liver disease. If spironolactone is used concomitantly, determine serum K^+ frequently; both can cause K^+ retention and elevated serum K^+. Two deaths have been reported with such concomitant therapy (in one, recommended dosage was exceeded, in the other serum electrolytes were not properly monitored). Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving Dyrenium® (triamterene, SK&F Co.), and leukopenia, thrombocytopenia, agranulocytosis, and aplastic anemia have been reported with thiazides. Do periodic blood studies in cirrhotics to check for nondrug-related variations in blood pictures, and in patients with folic acid depletion, since 'Dyrenium' may contribute to appearance of megaloblastosis. Antihypertensive effect may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances. Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and, rarely, allergic pneumonitis have occurred with thiazides alone.

Supplied: Bottles of 100 and 1000 capsules; Single Unit Packages of 100 (intended for institutional use only).

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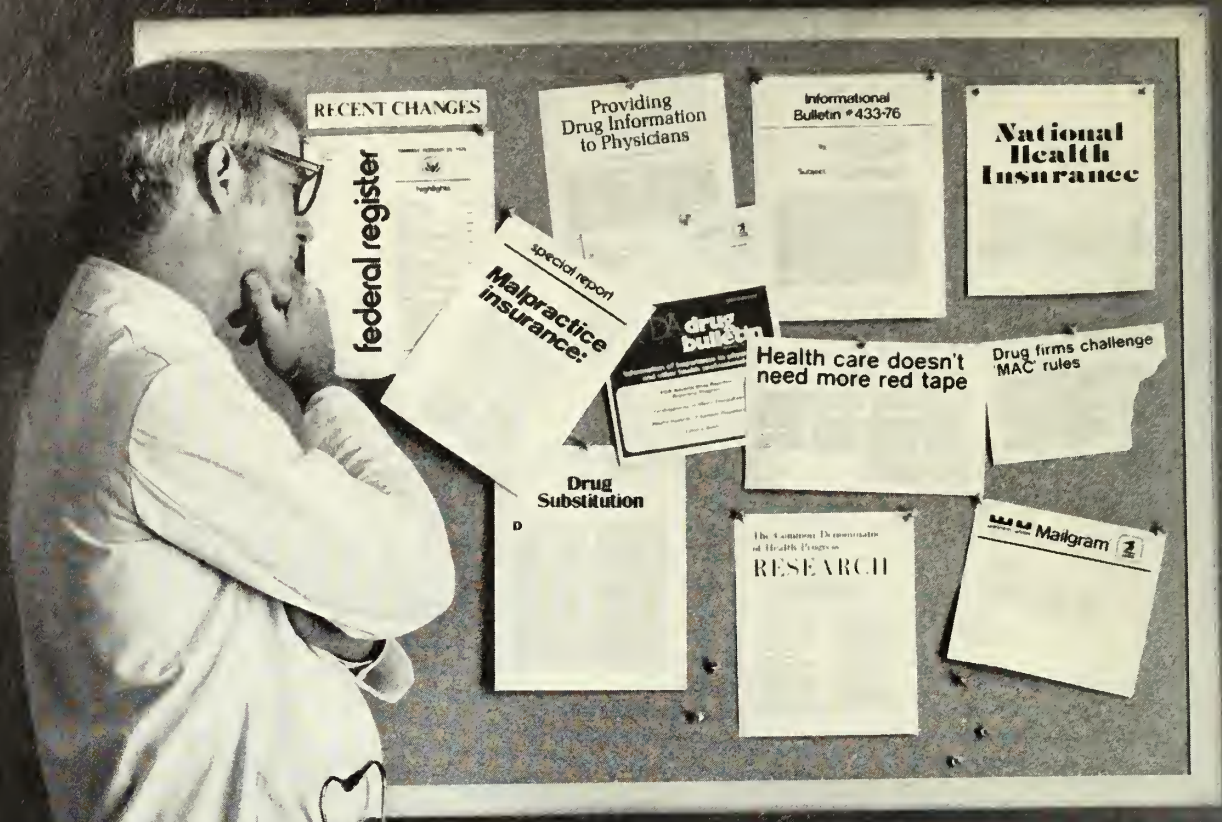
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THERE ARE A LOT OF PEOPLE GETTING BETWEEN YOU AND YOUR PATIENT.

Medicine today is in the spotlight, subjected to all kinds of scrutiny. Your control over patient therapy is being monitored, judged and occasionally abrogated, sometimes by unknown third parties.

The worry is that in the wake of this focus, the relationship between you and your patient will be weakened, without offsetting benefits. Consider three examples:

Drug substitution In most states, pharmacy laws, regulations or professional custom stipulate that your non-generic prescriptions be filled with the precise products you prescribe. But in the last five years, a dozen or more State laws have been changed, permitting the pharmacist in most cases to select a product of the same generic drug to fill any prescription.

Ironically, this dilution of physician control has taken place against a background of growing evidence that purportedly equivalent drug products may be inequivalent, since neither present drug standards nor their enforcement are optimal. In fact, the FDA itself says it has not enforced the same standards for hundreds of "follow-on" products that it had applied to the original NDA approvals. Thus physician control over patient therapy is being eroded with a risk that patients may be exposed to drugs of uncertain quality.

The major advertised claim for substitution is reduced prescription prices for consumers. Yet no documentation of any significant savings has been produced.

MAC Maximum Allowable Cost, MAC for short, is a Federal regulation designed to cut the Government's drug bill by setting price ceilings for drugs dispensed to Medicare and Medicaid patients. Unless the prescriber certifies on the prescription that a particular product is medically necessary, the Government intends to pay only for the cost of the lowest-priced, purportedly-equivalent, generally-available product. The effect of the program may be that elderly and indigent patients will be restricted to products which someone in Washington believes are priced right. Practicing doctors will have little to say about administration of the program, since Government will have absolute authority to make its choices stick.

The drug lag The future of drug and device research depends upon a scientific and regulatory environment that encourages therapeutic innovations. The American pharmaceutical industry annually is spending more than $1 billion of its own funds and evaluating more than 1,200 investigational compounds in clinical research. Disease targets include cancer, atherosclerosis, viruses and central nervous system disorders, among others. But there is a major barrier to the flow of new drugs to your patients: The cost of the research is more than ten times what it was, per product, in 1962; and whereas governmental clearance of new drug applications took six months then, it commonly consumes two years now.

The FDA needs adequate time, of course, to consider data. But it is equally clear that the present approval process contributes to needless delay of needed therapy. That's why the increased efficiency of the drug approval process is vital to all our futures.

If these issues concern you, we suggest that you make your voice heard—among your colleagues and your representatives in State legislatures and in Washington.

It could make a difference in your practice tomorrow.

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Average weight loss of 2.15 lbs per week compared in clinical studies against a placebo.

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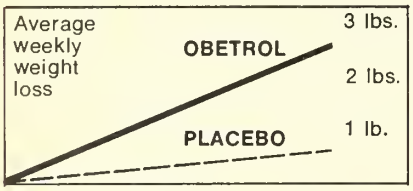

Obetrol eases the discomfort of adherence to a restricted diet in individuals who are well motivated to reduce their food intake.

Clinical studies disclose amphetamines to be the most dependable drug in a weight-reduction regimen compared to other anorexigenic agents.

Amphetamines have a significant potential for abuse. In view of their limited short-term anorectic effect and rapid development of tolerance, they should be used with extreme caution and only for limited periods of time in weight reduction programs.

Actions: Amphetamines are sympathomimetic amines with CNS stimulant activity. Peripheral actions include elevation of systolic and diastolic blood pressures and weak bronchodilator and respiratory stimulant action. The anorectic effect diminishes after a few weeks.

Indications: Exogenous obesity, as a short term (a few weeks) adjunct in a regimen of weight reduction based on caloric restriction. For patients in whom obesity is refractory to other measures.

Contraindications: Advanced arteriosclerosis, symptomatic cardiovascular disease, moderate to severe hypertension, hyperthyroidism, known hypersensitivity or idiosyncracy to the sympathomimetic amines. • Agitated states. • Patients with a history of drug abuse. • During or within 14 days following the administration of monoamine oxidase inhibitors, hypertensive crises may result.

Warnings: Tolerance to the anorectic effect usually develops within a few weeks. When this occurs, the recommended dose should not be exceeded in an attempt to increase the effect, rather, the drug should be discontinued. Amphetamines may impair the ability of the patient to engage in potentially hazardous activities such as operating machinery or driving a motor vehicle; the patient should therefore be cautioned accordingly.

Precautions: Caution is to be exercised in prescribing amphetamines for patients with even mild hypertension. Insulin requirements in diabetes mellitus may be altered in association with the use of amphetamines and the concomitant dietary regimen. Amphetamines may decrease the hypotensive effect of guanethidine. The least amount feasible should be prescribed or dispensed at one time in order to minimize the possibility of overdosage.

Adverse Reactions: *Cardiovascular:* Palpitation, tachycardia, elevation of blood pressure. Central nervous system: Overstimulation, restlessness, dizziness, insomnia, euphoria, dysphoria, tremor, headache; rarely, psychotic episodes at recommended doses. *Gastrointestinal:* Dryness of the mouth, unpleasant taste, diarrhea, other gastrointestinal disturbances. Anorexia and weight loss may occur as undesirable effects when amphetamines are used for other than the anorectic effect. *Allergic:* Urticaria. *Endocrine:* Impotence, changes in libido.

Dosage and Administration: Regardless of indication, amphetamines should be administered at the lowest effective dosage and dosage should be individually adjusted. Late evening medication should be avoided because of the resulting insomnia.

1. Narcolepsy: Usual dose 5 to 60 milligrams per day in divided doses.
2. Minimal brain dysfunction:
   a. Not recommended for children under 3 years of age.
   b. Children from 3 to 5 years of age: 2.5 milligrams daily, raised in increments of 2.5 milligrams at weekly intervals until optimal response is obtained.
   c. Children 6 years of age and older, 5 milligrams, once or twice daily, increased in increments of 5 milligrams at weekly intervals. Only in rare cases will it be necessary to exceed a total of 40 milligrams per day.
3. Obesity: Usual adult dose 5 to 30 milligrams per day in divided doses.

Overdosage: Manifestations of acute overdosage with amphetamines include restlessness, confusion, assaultiveness, hallucinations, panic states. Fatigue and depression usually follow the central stimulation. Cardiovascular effects include arrhythmias, hypertension or hypotension, and circulatory collapse. Gastrointestinal symptoms include nausea, vomiting, diarrhea, and abdominal cramps. Fatal poisoning usually terminates in convulsions and coma.

Management of acute amphetamine intoxication is largely symptomatic and includes lavage and sedation with a barbiturate. Experience with hemodialysis or peritoneal dialysis is inadequate to permit recommendations in this regard.

Availability: Supplied in bottles of 100; 500 and 1,000 tablets.

CAUTION: FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION.

January 1973

Comprehensive informational brochure available upon written request. Prescribe Obetrol for appetite control.

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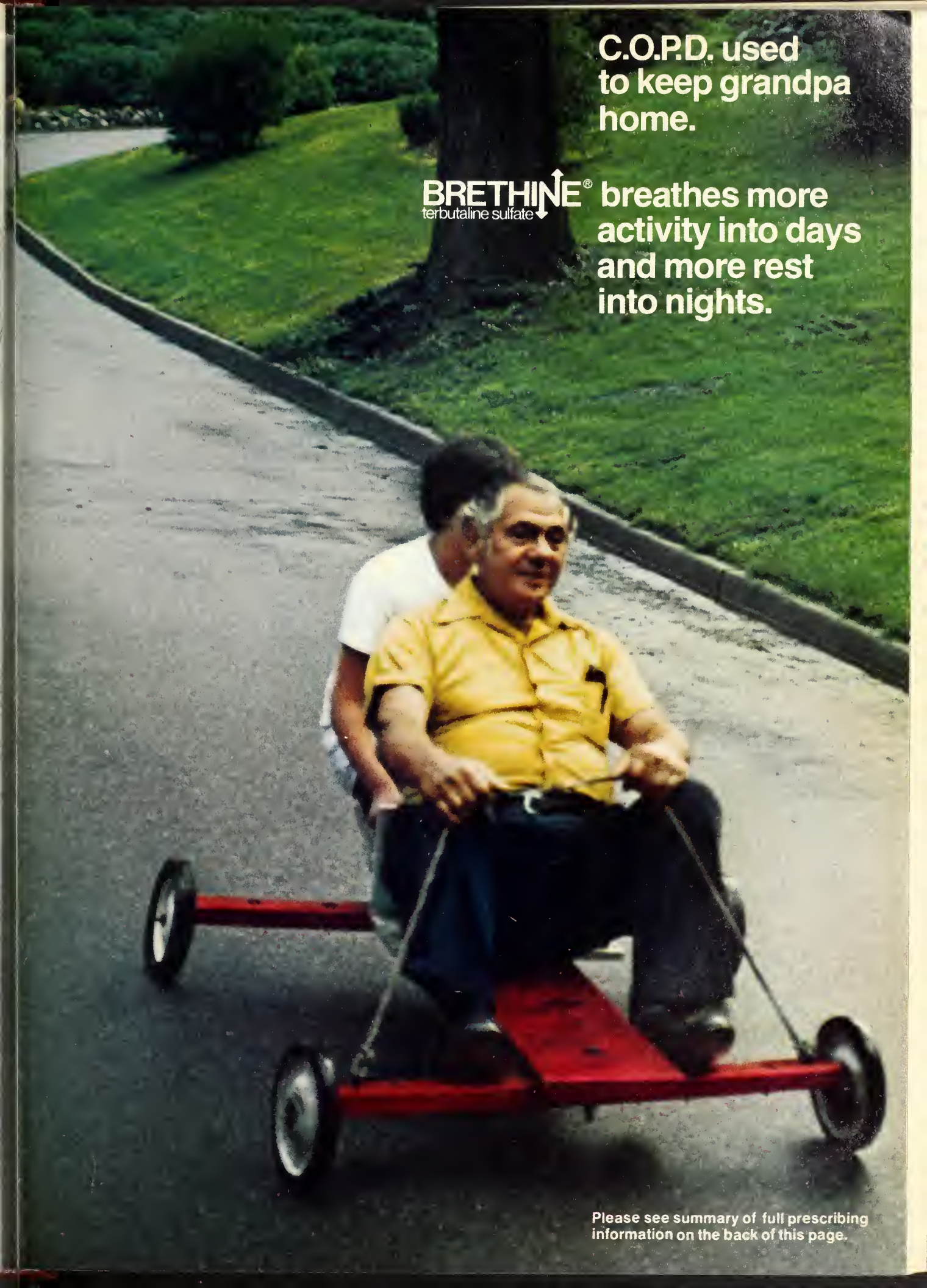
C.O.P.D. used to keep grandpa home.
BRETHINE®
terbutaline sulfate
breathes more activity into days and more rest into nights.
Please see summary of full prescribing information on the back of this page.

BRETHINE®
terbutaline sulfate

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Almost twice as effective as some other bronchodilators.

Brethine 5 mg was almost twice as effective as aminophylline 400 mg in a single-dose study. Brethine is twice as effective as ephedrine. And it has been shown to be more effective than metaproterenol.

If Brethine is added to theophylline, dosage should be titrated. Tablets of 2.5 mg and 5 mg are available.

Action may last up to 8 hours in some patients.

Brethine can provide more comfortable breathing with one tablet at bedtime, upon arising, and at midafternoon (at approximately six-hour intervals). Brethine contains no respiratory depressants (tranquilizers, sedatives or alcohol).

Minimal cardiac effect.

Brethine produces proportionally greater changes in pulmonary function than in heart rate or blood pressure.

Note: Patients should be advised that they may experience mild tremor when Brethine therapy is initiated.
With continued therapy, tremor usually diminishes while bronchodilation remains highly effective.

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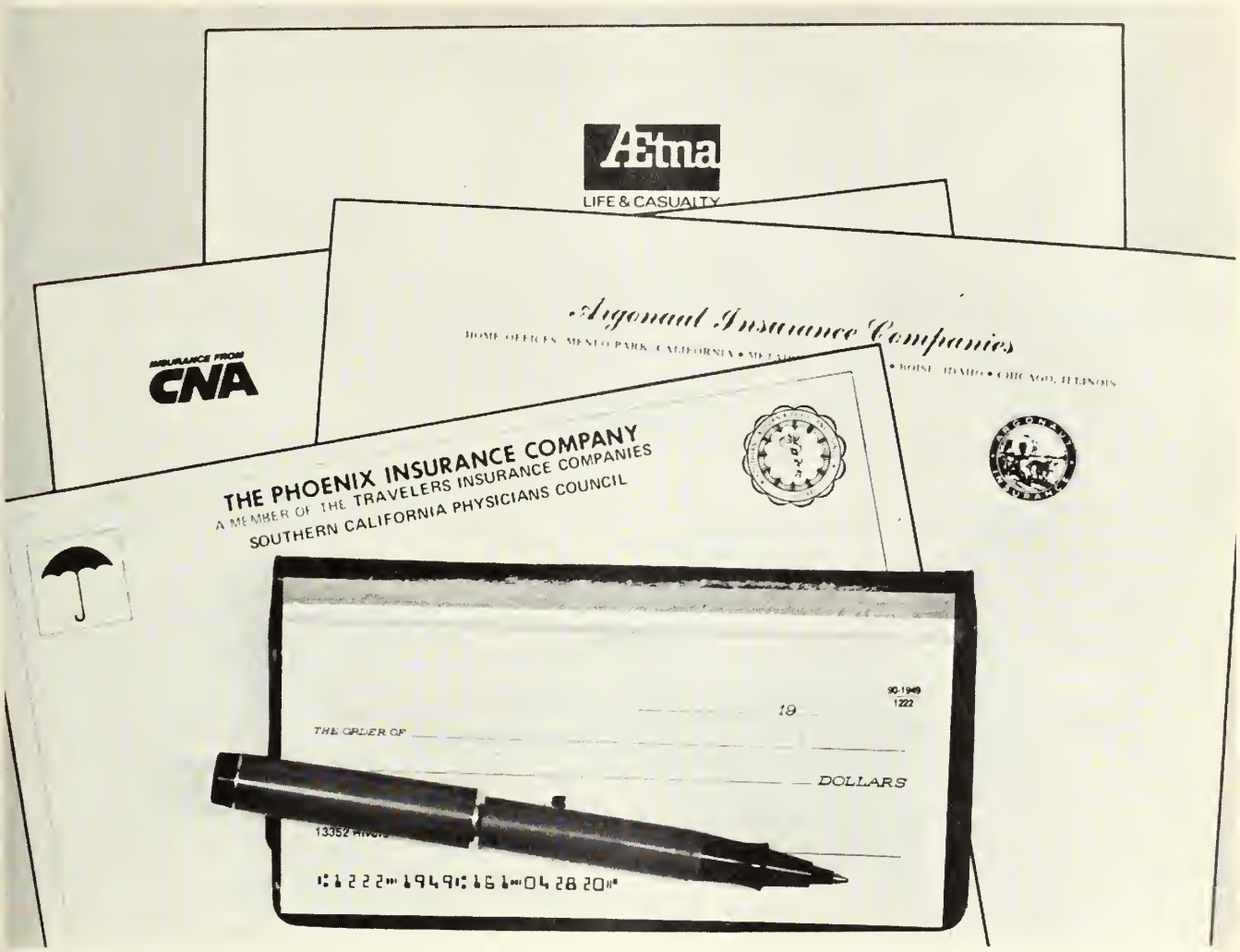

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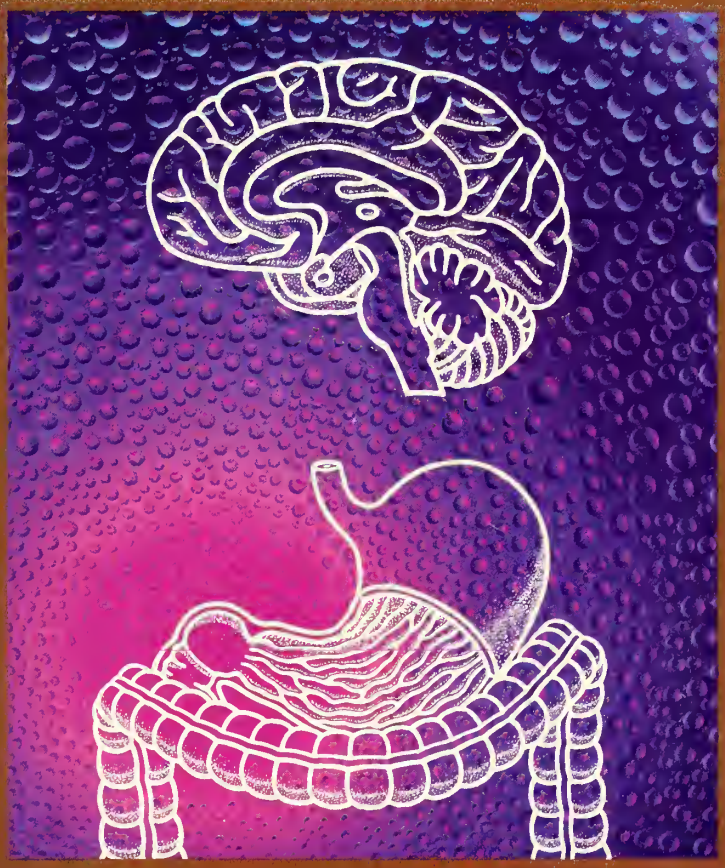

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Refer to: Baydur A: The spectrum of extrapulmonary tuberculosis.
West J Med 126:253-262, Apr 1977

The Spectrum of Extrapulmonary Tuberculosis

AHMET BAYDUR, MD, *Downey, California*

The incidence of new cases of extrapulmonary tuberculosis has remained constant, despite the decline in new cases of active pulmonary tuberculosis. This might be due to a delay in recognition, and particularly a lack of consideration of tuberculosis when the presenting symptoms are other than respiratory. Extrapulmonary tuberculosis should be considered in the differential diagnosis of bone, joint, genitourinary tract and central nervous system (CNS) diseases.

To determine factors that might delay recognition and identification, 62 patients having extrapulmonary tuberculosis during 1969-1972 at the Los Angeles County-University of Southern California Medical Center were studied.

Three quarters of these patients had had CNS, skeletal or genitourinary tuberculosis in equal distribution or 25 percent each. CNS involvement was seen frequently in the disseminated form. Presenting symptoms were protean and not specific, such as fever, anorexia, weight loss, cough, lymphadenopathy and neurologic abnormalities. Roentgenograms of the chest were abnormal in most. When a roentgenogram of the chest suggests pulmonary tuberculosis, signs and symptoms in other body systems should suggest extrapulmonary tuberculosis. If no abnormalities are seen on a roentgenogram of the chest, however, this does not preclude the diagnosis of extrapulmonary tuberculosis. Neither does a negative tuberculin skin test exclude the condition.

Abnormal laboratory findings are common, especially in disseminated tuberculosis. These include various anemias, bone marrow disorders, hyponatremia due to inappropriate antidiuretic hormone syndrome. Analyses of pleural, peritoneal, pericardial and joint fluid usually show an exudate high in lymphocytes and occasionally low in glucose. Similar findings are seen in spinal fluid. The histological features of caseous or noncaseous granulomas are suggestive of but not specific for tuberculosis. Only culture of mycobacteria from sputum, urine, spinal fluid, pleural and other effusions and tissue biopsy specimens will yield a definitive diagnosis.

Physicians must have a high index of suspicion to diagnose extrapulmonary tuberculosis, as it can resemble any disease in any organ system. Immediate therapy in the disseminated variety, sometimes even before a definite diagnosis can be made, may be lifesaving.

ABBREVIATIONS USED IN TEXT
ADH = antidiuretic hormone
CSF = cerebrospinal fluid
LAC-USC = Los Angeles County-University of Southern California (Medical Center)
PAS = para-aminosalicyclic acid
PPD = purified protein derivative

THE INCIDENCE OF PULMONARY TUBERCULOSIS throughout the United States is declining. The annual number of newly reported cases of pulmonary tuberculosis nationally decreased from 49,203 in 1963 to 27,051 in 1973, a decrease of nearly 50 percent.[1] Major factors for this decline are thought to be improving social conditions, as well as the use of potent chemotherapeutic agents.

However, extrapulmonary tuberculosis has not had a similar rate of decrease. According to the United States Public Health Service, for the same ten year period, 1963-1973, the annual number of newly reported cases has remained at around 4,000 per year.[1] The incidence of extrapulmonary cases of new active cases of tuberculosis rose from 7.6 percent in 1962 to 11.8 percent in 1973. There are several explanations for this:

- Increased recognition and reporting of extrapulmonary tuberculosis.
- Current "overdiagnosis" of extrapulmonary tuberculosis.
- An actual increase in the incidence of extrapulmonary tuberculosis.
- A combination of all these factors.

Extrapulmonary tuberculosis has protean manifestations. The clinician must keep this in mind when a patient presents with a wide variety of signs and symptoms. For example, tuberculosis remains as the most important cause of fever of unknown origin.[2] Also, manifestations referable to any organ system or multiple organ systems can be secondary to tuberculosis involvement.

In order to examine manifestations of extrapulmonary tuberculosis in the setting of a large county hospital, a retrospective study was undertaken of 62 patients who were admitted to the Los Angeles County-University of Southern California (LAC-USC) Medical Center in whom a diagnosis was eventually made. The study was done to:

- Determine the distribution of the patients by age, race and sex;
- Identify major symptoms;
- Determine clinical findings;
- Establish the site of material yielding positive cultures for tubercle bacilli, and therefore exact diagnosis of tuberculosis, and the frequency of obtaining such cultures;
- Examine biopsy data;
- Based on above data, determine frequency of extrapulmonary involvement;
- Identify disorders associated with the extrapulmonary tuberculosis;
- Collect and study autopsy results, and
- Follow-up results in survivors.

Methods

The records of 62 adult and pediatric patients admitted during 1969-1972 to LAC-USC Medical Center with a discharge diagnosis of extrapulmonary tuberculosis were reviewed.

The diagnosis of extrapulmonary tuberculosis included the following criteria:

- Culture proof of infection with Mycobacterium tuberculosis.
- Biopsy or necropsy material demonstrating caseating granulomas with acid-fast bacilli.
- The presence of a miliary pattern on chest roentgenogram.
- Clinical presentation and manifestations consistent with tuberculosis, with improvement after antituberculous therapy.

All but four patients fulfilled the first criterion and one or more of the others. In four patients in whom culture evidence was lacking, two or more of the remaining criteria were present.

Results

Incidence, Age, Sex and Race

The distribution of patients by age, sex and race is shown in Table 1. The age range was four months to 96 years. Fifty-six percent (35 of 62) of the patients were males with predominant clustering during the third through fifth decades. The peak incidence for females was in the third decade. Eight males and seven females were less than 16 years of age.

Fifty-six percent (35 of 62) of the group were of Spanish-American descent, despite the fact that only 24 percent of total admissions to the medical center during the same period were of

Based on work as Fellow in Pulmonary Disease, Los Angeles County-University of Southern California Medical Center, 1973-1975. Dr. Baydur is now Visiting Assistant Professor of Medicine, University of Southern California—Rancho Los Amigos, Downey, California.

Submitted, revised, August 1, 1976.

Reprint requests to: Ahmet Baydur, MD, Pulmonary Disease Service, Rancho Los Amigos Hospital, 7601 East Imperial Highway, Downey, CA 90242.

TABLE 1.—*Distribution of 62 Patients by Age, Sex and Race*

Age	*Male*	*Female*
1 - 12 mos.	2	2
1 - 15 yrs.	6	5
16 - 20	..	2
21 - 30	9	8
31 - 40	5	3
41 - 50	6	4
51 - 60	3	2
61 - 70	2	1
71 - 100	1 (96)	1
	34	28

Spanish-American	35
Black	15
Caucasian	6
Oriental	4
Indian	2

this racial group. Conversely, 24 percent of the patients were black during a period when 30 percent of total hospital admissions were of this race.

Presenting Symptoms

Predominant symptoms (see Table 2) included fever, anorexia, cough and weight loss. The greatest incidence of any one symptom was 33 percent. Part of the reason for this finding may be lack of reporting due to patients not mentioning symptoms or physicians not recording them.

Duration of symptoms was quite variable, ranging from one day to several months before the patient sought medical attention.

Presenting Clinical Findings

Fever was the most commonly reported clinical finding (see Table 3), occurring in a little over a third of the cases. The relatively high incidence of neurologic signs can be attributed to the fact that 25 percent of the patients had tuberculous meningitis.

Associated Disorders and Predisposing Conditions

Chronic alcoholism (7 of 62 cases, or 11 percent), either with or without recognized liver disease, constituted the most significant of all associated disorders (see Table 4). A previous history of tuberculosis was recorded in eight of the 62 cases. Information was not adequate to evaluate previous antituberculous therapy.

In 44 of the 62 cases (71 percent) there were no serious underlying conditions. Predisposing factors such as steroid therapy, gastrectomy, carcinoma, blood dyscrasias or hypogammaglobulinemia were not seen.

Diagnostic Procedures

Skin tests of 33 patients were carried out with an intermediate strength (5 TU) purified protein derivative (PPD); 26 (79 percent) were positive (greater than 9 mm of induration). In one patient who eventually died with tuberculosis meningitis there was no reaction to an intermediate strength PPD skin test, but there was response to a second strength (250 TU) skin test.

Of 48 chest roentgenograms recorded at admission, 40 were abnormal (83 percent). There was no consistent pattern; parenchymal infiltrates, hilar and mediastinal adenopathy, and pleural effusions were noted in equal number. Fibrocalcific lesions were common in patients with previous history of tuberculosis.

Only five chest roentgenograms showed a miliary pattern. This contrasted with three cases of miliary dissemination found at necropsy, only one of which showed a miliary radiographic pattern.

Culture Data

Table 5 shows culture results obtained in 56 of 62 patients. Of 52 survivors, there were posi-

TABLE 2.—*Major Symptoms in 62 Patients*

Symptom	*Number of Patients*
Fever	21
Urinary symptoms	14
Anorexia, nausea, vomiting	13
Cough	13
Altered sensorium	10
Weight loss	9
Flank, back pain	9
Neck swelling	9
Back (paraspinal) swelling	8
Headache	6
Seizures	6
Weakness	5
Chills	5
Sweats	5
Swollen joints	4
Diarrhea	4
Abdominal pain	3
Dyspnea	3
Chest pain	3
Sore throat	3
Hoarseness	2
Hemoptysis	2
Abdominal swelling	2
Flank swelling	2
Scrotal swelling	2
Hip pain	2
Failure to thrive	2
Menometrorrhagia	2
Eye complaints	2
Ear complaints	1
Ankle edema	1

tive cultures in 47. The combination of sputum and gastric aspirate cultures yielded a bacteriologic diagnosis of tuberculosis in 20 survivors (37 percent). Urine cultures were positive in eight survivors (15 percent). Cerebrospinal fluid contributed a significant source of positive cultures (ten of 62 patients or 16 percent).

Biopsy Data

Lymph nodes and bone marrow biopsy specimens (see Table 6) together made up 16 of 28 biopsy specimens (57 percent) that yielded granulomas. This can be explained by the ready accessibility of these sites. Surprisingly, no liver biopsies were recorded in the 62 patients.

Clinical Involvement Based on All Antemortem Methods

Table 7 shows extrapulmonary involvement as determined by antemortem methods in the 62 patients. Fifteen patients had tuberculous meningitis. Ten cases of the disease were proven by cerebrospinal fluid (CSF) culture and the remainder were diagnosed using neurologic findings, in association with abnormal chest roentgenograms, abnormal CSF chemical and cellular findings, and positive cultures obtained in other body fluids. Pleocytosis was found in 12 patients, with cell counts ranging from 23 to 2,100 cells per ml; in 11 patients there were CSF protein values of greater than 50 mg per 100 ml. CSF glucose levels were less than 50 mg per 100 ml in ten patients.

Genitourinary tuberculosis was diagnosed in 15 patients during life. Six of these had complained of dysuria and frequent urination, while eight had hematuria. In eight patients the kidney

TABLE 3.—*Clinical Findings in 62 Patients*

Sign	*Number of Patients*
Fever (>99° F.)	22
Neurologic signs	14
Palpable adenopathy	13
Meningismus	8
Ausculatory findings	7
Back (paraspinal) swelling	6
Abdominal and costovertebral-angle tenderness	5
Hydrocephalus	5
Pleural effusion (radiograph)	4
Papilledema	4
Ascites	3
Scrotal mass	3
Swollen joint or limb	3
Abdominal or pelvic mass	2
Spinal abnormalities (radiographic)	2
Draining fistula	2
Hypothermia (<97° F.)	1
Splenomegaly	1
Abnormal pelvic examination (tender adnexa)	1
Clubbing	1
Edema	1
Cellulitis	1
Laryngeal abnormalities	1
Pericardial effusion	1
Eye findings	1

TABLE 4.—*Associated Conditions Not Directly Related to Tuberculosis*

Condition	*Number of Patients*
Liver disease	4
Renal disease	4
Seizure disorder	4
Amebiasis	3
Alcohol abuse	2
Cholelithiasis	2
Diabetes mellitus	2
Heroin abuse	1
Chronic obstructive pulmonary disease	1
Cerebrovascular disease	1
Discoid lupus	1
Multiple congenital anomalies	1
Sickle cell disease	1
Disseminated aspergillosis	1
History of old coccidioidomycosis	1
Hypergammaglobulinemia	1

TABLE 5.—*Frequency and Site of Material Yielding Positive Cultures*

Site	*Number*
Sputum	12
Cerebrospinal fluid	10
Urine	9
Lymph node (Extrathoracic)	8
Gastric aspirate	8
Bone marrow	7
Endometrium	3
Ascitic fluid	2
Joint fluid	2
Paraspinal "cold" abscess	2
Fistula	1
Brain abscess	1
Pericardial fluid	1
Eye structures	1

TABLE 6.—*Number of Patients with Granulomas Demonstrated on Biopsy*

Source	*Number of Patients*
Lympth node	9
Bone (marrow) biopsy	7
Endometrium	3
Bladder	2
Genital structures (male)	2
Kidney	1
Peritoneum	1
Brain abscess	1
Eye structures	1
Laryngeal structures	1

and bladder alone were involved, in one the male genitalia and in three the endometrium alone. In three males, there was involvement of both the kidneys and genitalia.

Of six patients in whom pyelograms were done, abnormalities were noted in all. In five of the 15 patients with genitourinary tuberculosis there was a history of pulmonary tuberculosis, the highest incidence seen in patients with extrapulmonary complications.

Tuberculous osteomyelitis was seen in 15 patients. Eleven of these cases involved vertebrae. Ten of these patients had complaint of back pain. In addition, in eight of them there was swelling over or about the involved area. Symptoms often antedated radiographic changes by months. Radiologic abnormalities were seen in all patients with tuberculous osteomyelitis, primarily consisting of lytic lesions. Narrowing of the intervertebral space was also seen in patients with vertebral tuberculosis (Pott's disease). In two patients spinal deformities were noted and in three there was paraplegia secondary to involvement of the spinal cord.

TABLE 7.—*Extrapulmonary Involvement in 62 Patients as Determined by Antemortem Methods*

Site	*Number of Patients*
Meninges	15
Bone (mostly vertebra)	15
Lymph nodes	9
Urinary tract	8
Genital structures (male)	4
Endometrium	3
Retroperitoneal mass (abscess)	3
Pericardium	2
Joints	2
Eye	2
Larynx	1
Peritoneum	1
Brain (abscess)	1

TABLE 8.—*Organ Involvement as Determined in Seven Necropsies*

Site	*Number*
Central nervous system	6
Lung	5
Liver	4
Peritoneum	4
Lymph nodes	3
Spleen	3
Marrow	3
Kidneys	3
Pleura	2
Gastrointestinal tract	2
Adrenals	1

Treatment

In all, 56 patients received some form of antituberculosis chemotherapy. Six patients died before a diagnosis could be made; hence, died without therapy. Three more died while therapy was being given.

A combination of streptomycin, isoniazid, and para-aminosalicylic acid (PAS) was given to 35 patients as initial therapy. Isoniazid was the most commonly used drug, employed in 51 cases as first-line therapy. Streptomycin was used next most commonly in combination (46 cases) with isoniazid. PAS (35 cases) and ethambutol (19 cases) were also used together with isoniazid. Four patients in addition received second-line drugs (cyloserine, viomycin and ethionamide) when initial drug resistance was encountered. Corticosteroids were used in one case of meningitis. Surgical therapy was a common adjunct, used particularly in tuberculous osteomyelitis and in spinal cord involvement, where laminectomy and spinal fusion were most commonly done.

Morbidity and Mortality

There were ten deaths, all in hospital. Of 24 patients who maintained follow-up clinic contact, all were alive with varying sequelae after six months. Six of the ten patients who died were of Spanish-American origin; two were black.

There were seven necropsies (Table 8). Three showed a miliary dissemination throughout the lungs, and hematogenous involvement of major organ systems. In five cases the lung was noted to be the primary source of infection. The central nervous system, lymphatic system, liver and peritoneum were the most commonly involved extrapulmonary sites. Conditions found at autopsy in addition to tuberculosis included hepatic failure, chronic renal disease, diabetes mellitus, sickle cell disease and aspergillosis. Clinical and pathologic findings in the seven necropsies are summarized in Table 9.

Discussion

The principal portal of entry for Mycobacterium tuberculosis is the respiratory tract. This can result in either widespread dissemination or localized areas of involvement in various organs.[3,4] Clinical manifestations of localized areas of infection may become apparent after long periods of quiescence. Consequently, latent foci of infection are of great importance in the de-

TABLE 9.—*Findings in Seven Necropsies in Patients Who Died with Extrapulmonary Tuberculosis*

Case	*Age and Sex*	*Days of Illnesses Before Death*	*Days of Anti-TB Treatment*	*Lungs*	*Liver*	*Lymph Nodes*	*Spleen*	*Kidneys*
1 Spanish-American	34 ♀	34	20	Caseating granulomata, bronchopneumonia, pleuritis with effusion, positive culture	Massive necrosis (drug induced?)	....	....	....
2 Spanish-American	45 ♂	5 hrs.	0	Caseating granulomata, cavitary TB, TB pneumonia, pleuritis, multiple pulmonary abscesses, positive culture	Minimal periportal fibrosis	Caseating granulomata	....	....
3 Oriental	37 ♂	12	0	....	....	....	....	....
4 White	18 ♀	6	0	Caseating granulomata, pneumonic spread, positive culture	Caseating granulomata	Caseating granulomata	Caseating granulomata	Caseating granulomata
5 Black	21 ♂	96	85	Granulomatous cavitation with *Candida* and *Aspergillus* in tissue and in culture, infarct with fungal thrombi	....	....	....	....
6 Black	73 ♀	23	14	Caseating granulomata, positive culture, emphysema	Caseating granulomata	Noncaseating granulomata	Noncaseating granulomata	Caseating granulomata
7 Spanish-American	60 ♀	1	0	Caseating granulomata, thrombo and fat emboli +AFB, positive culture	Noncaseating granulomata	Caseating granulomata	Noncaseating granulomata	Noncaseatin granulomata

+AFB = acid-fast bacilli seen on tissue

velopment of most types of extrapulmonary tuberculosis.

Possibly one exception to this pathogenesis is seen in gastrointestinal tuberculosis. Unpasteurized milk can be a source of bowel involvement with bovine M. tuberculosis, but it has declined to a point of near nonexistence in this country because of pasteurization. Isolated cases still encountered today are thought to result from swallowing infected sputum. None of these cases are due to Mycobacterium bovis.

Extrapulmonary tuberculosis is not necessarily a disease of the elderly. Tuberculous meningitis and lymphadenitis were noted in a sizable younger population in this study, as it has in many others (69 percent less than 40 years of age). Indeed, before effective public health control, measles and whooping cough were thought to predispose to miliary tuberculosis.[5,6] Most series, however, cite a trend towards older age groups, as people continue to survive into an older age when degenerative diseases such as arteriosclerotic heart disease, diabetes mellitus, alcoholism and malignancies play a role in suppressing most defense mechanisms.[1,2,5-7] Interestingly enough, in our study there were nearly

drenals	Central Nervous System	Heart	Other	Clinical Comments
.	Caseating granulomata, meninges	....	Caseation, omentum with small bowel perforation; gastric ulceration; positive culture endometrium	Headache, confusion, lethargy, abdominal pain; findings of meningitis, hydrocephalus by angiography. Positive skin test; abnormal chest roentgenogram; deterioration following shunt procedure, liver failure, pneumonia, electrolyte imbalance, anemia.
.	....	....	Microgranulomata, appendix; laryngotracheobronchitis; cholelithiasis; cholecystitis	Chronic alcoholism; respiratory distress, abnormal chest roentgenogram, serosanguinous pleural fluid, anemia; shock
.	Caseating granulomata, abscess, right cerebrum, positive culture	....	Pulmonary congestion; generalized arteriosclerosis; nephrosclerosis; pyelonephritis; uricolithiasis; gastric ulceration; lymphoid hyperplasia, small bowel; pancreatic lipomatosis; cholelithiasis	3-week history headaches, incoordination, weakness, (L) hemiparesis, impaired gait, mental retardation, multiple congenital anomalies, cholelithiasis, hypertension, pyelonephritis, polycythemia, abnormal spinal tap. Abnormal chest roentgenogram. Skin test not reported.
.	Caseating granulomata, positive culture, meninges, spinal cord	....	Caseation granulomata; abscess vertebra; positive culture; psoas abscess	2-week history backache, malaise, fever, hematuria, dysuria, weight loss; papilledema, costovertebral-angle tenderness. Abnormal spinal tap. Progressive paraplegia. Blocks at cervical vertebra 6 and lumbar vertebrae 1,2. All cultures negative during life. Following laminectomy, progressive deterioration with respiratory failure. Skin test and chest roentgenogram not reported.
Steroid induced atrophy	Spinal myelitis with cord compression	....	Skin: Candida invasion; larynx: Candida invasion; marrow: sickling; stomach: Candida	Sickle cell disease. 3-month history back and chest pain, weight loss, fever, sweats. Mediastinal mass, supraclavicular adenopathy, paravertebral mass on roentgenogram with involvement thoracic vertebrae 2,3; progressive paraplegia, incontinence, leukopenia; steroid induced diabetes mellitus, hyperosmolar coma, sepsis, metabolic acidosis, respiratory distress and failure. Negative chest roentgenogram, negative skin test. Lytic lesion rib, +AFB in bone, but negative culture.
.	Noncaseating granulomata, meninges	Focal areas lymphocytic myocarditis (early granulomas?)	Caseating granulomata marrow; leiomyoma stomach; pancreatic fibrosis	Diabetes mellitus; dehydration, confusion, ketonuria; fever, abdominal mass, urinary tract infection; hyponatremia. All cultures negative during life. Negative chest roentgenogram. Negative skin test.
Caseating granulomata	Caseating granulomata, abscesses, cerebrum, cerebellum, pons	....	Noncaseating granulomata marrow; Noncaseating granulomata peritoneum	Diabetes mellitus; chronic renal disease, seizure disorder; dehydration, confusion, agitation, abnormal spinal tap. Abnormal chest roentgenogram; skin test not reported.

twice as many men over 40 years of age than women, an observation similar to those made by others.[1,7,8]

Of great importance is the fact that persons of Spanish-American descent had a significantly high incidence of extrapulmonary tuberculosis. The reasons for this high incidence have been controversial. A possible racial or genetic predisposition has been postulated for non-Caucasian races.[4] However, socioeconomic conditions in Latin America and among Latin Americans in the United States are probably the major contributing factor. The base incidence of tuberculous infection as determined by skin testing is higher in Latin American countries. This would also result in a higher morbidity. Recent estimates indicated that there were 180,000 new cases among a total population of about 285 million in Latin America and the Caribbean,[9] a rate five times greater than that found in the United States.

In addition, several investigators have noted the adverse influence of immigration on the incidence of tuberculosis. For example, persons born in North America and foreign-born segments of the population which constitute only about a fourth of the population, contribute equal num-

bers of infected cases. Immigrants tend to be under the age of 45 and thus tuberculosis tends to occur in the younger age groups as opposed to members of the host population who tend to acquire the disease at a later age. Immigration also increases the rate of tuberculosis in the native population of similar ethnic origin who commonly have the most interaction with the newcomers.[10]

Other investigators have also found that non-Caucasian races have significantly high incidences of extrapulmonary tuberculosis, especially of the miliary variety. These include blacks and American Indians.[1,7,8,11,12]

Predisposing factors such as alcoholism, alcoholic liver disease, diabetes mellitus, renal failure and cerebrovascular disease were commonly seen among patients as the LAC/USC Medical Center. Amebiasis and various disseminated fungal disorders were also noted, particularly among non-Caucasians. Although there were no examples in this study, one should keep in mind that disseminated tuberculosis has also been associated with neoplasms, blood dyscrasias, prolonged steroid therapy, and previous gastrectomy.[4,7]

Symptoms are protean and nonspecific. These include weakness, anorexia, fatigue, weight loss and cough. Fever of unknown origin should always suggest the possibility of tuberculosis. Altered sensorium and headache were common presenting symptoms of meningitis in this and other studies.[7,8]

Tuberculosis of the spine frequently presents with back pain with or without swelling. However, painless paravertebral swelling should raise the suspicion of tuberculous paravertebral abcess. A "cold abscess" can arise either from vertebral osteomyelitis which extends directly into surrounding soft tissues, or indirectly from a fistulous tract burrowing to the surface from a psoas abscess which points in the groin. Some workers feel that Pott's abscess may be a lymph-borne sequela of tuberculous pleuritis.[12] Radiographic changes are late and include intervertebral narrowing and bony destruction of the vertebral body. Occasionally, a paravertebral mass can be seen on chest or abdominal roentgenogram.

A positive skin test certainly supports the diagnosis of Pott's disease. On the other hand, a negative skin test does not exclude the presence of a tuberculous infection. In as many as 18 percent of a group of patients with a confirmed diagnosis of tuberculosis there can be a failure to react to an intermediate strength skin test.[13] Likewise, a variety of other pathogens can give rise to paravertebral masses such as staphylococci, Gram-negative bacilli, deep mycoses, sarcoidosis and metastatic carcinoma.[12] Therefore, the diagnosis should always be confirmed by culture material obtained by needle aspiration or by open biopsy. Because of the frequency of renal involvement in association with retroperitoneal abscess, urinalysis is also helpful.

Even if the aspirated material is negative for mycobacteria, the combination of localized pain or swelling, a positive skin test, and typical radiographic changes is strongly suggestive of tuberculous osteomyelitis. Hence, a trial of antituberculous medication is strongly indicated and may avoid the need for subsequent surgical intervention.

The high incidence of bone involvement from an old tuberculous source is thought to be due to its rich vascular supply. This accounts for the early involvement of the metaphyseal and epiphyseal areas of long bones. Involvement of subchondral bone can then lead to rupture into the joint space and to arthritis. As noted in this study, tuberculous arthritis tends to be monoarticular, and usually occurs in males of dark skinned races. Symptoms include pain and swelling of the involved joint. Radiographic changes include joint space narrowing, bony erosions and cysts. The definitive diagnosis can be made by synovial fluid aspiration and membrane biopsy. Although acid-fast bacilli are seen in only 25 percent, granulomas can be shown to be present in about two thirds of the cases.

As in other forms of extrapulmonary tuberculosis, genitourinary tuberculosis may also occur 20 or more years after the primary pulmonary infection. Abnormal findings on a roentgenogram, of the chest, positive skin test and microscopic hematuria or pyuria may be all that is necessary for a diagnosis of genitourinary tuberculosis.[14] Urine cultures are positive in most patients and in roughly two thirds there will be abnormal excretory urograms. Even a plain abdominal roentgenogram may show calcifications. Hypertension is rarely seen in this disorder.

Tuberculous pericarditis can result from extension from mediastinal lymph nodes or contiguous tuberculous pleuritis. There is an outpouring of a clear exudate, formation of granulomas and subsequent fibrosis. The signs and symptoms are those of chronic pericardial tamponade, with

hepatomegaly, edema, friction rub, enlargement of cardiac shadow on chest roentgenogram during the active phase, and constriction during the phase of fibrosis. The diagnosis is made by aspiration of pericardial fluid. Resection of part or all of the pericardium may be necessary for diagnosis, or for relief of tamponade.

Tuberculous peritonitis is most often seen in disseminated tuberculosis. Occasionally, the bacilli can spread through the wall of infected bowel, or from mesenteric nodes. Peritoneal tuberculosis occurs with greatest frequency in alcoholics and cirrhotics. Tuberculous peritoneal fluid has a high protein level, lactic dehydrogenase (LDH) content, and shows a predominance of lymphocytes. Definitive diagnosis can best be made with an open peritoneal biopsy. This is safer than a Cope biopsy which has been associated with several deaths due to blood loss, in clear contrast to pleural biopsy.[15] Intestinal perforation may also occur with the Cope needle. It should be used only when significant ascites is present and preferably in the absence of abdominal adhesions. Peritoneoscopy can be helpful but requires specially trained personnel. Laparotomy may be required for definitive diagnosis, especially in cases involving obstruction or perforation.[15]

As in the above cases, the most useful adjunctive aid in the clinical diagnosis is a roentgenogram of the chest. The 41 roentgenograms of the chest showing abnormalities in this study yielded a wide variety of findings. These included paratracheal and hilar adenopathy, air-space filling infiltrates, calcified Ghon complexes and miliary patterns. A miliary pattern, however, may not be apparent until weeks after the patient is seen. Unfortunately, other disorders can also give rise to a miliary radiographic appearance. These include sarcoidosis, pneumoconiosis, metastatic carcinoma, and fungal and viral infections. Also, its absence does not exclude the diagnosis of miliary tuberculosis.

The intermediate strength PPD test (5 TU) is a useful epidemiological tool for population studies to estimate true tuberculous infection and infection with other mycobacterial species. It will yield positive results in about 80 percent of cases of localized extrapulmonary tuberculosis. The incidence of positive reactions in patients with disseminated tuberculosis is also high;[7,13] however, a negative skin test implies a poor prognosis, as it did in this study. If the 5 TU test is negative in a patient critically ill with tuberculosis or other diseases, it should be followed by a second strength (250 TU) skin test.

Other clinical findings that are associated with tuberculosis not yet mentioned can be helpful but are not specific in diagnosing extrapulmonary tuberculosis. A host of hematologic abnormalities, including various forms of anemia; leukemoid reactions; marrow hypoplasia with granulocytosis and thrombocytopenia; myelofibrosis, and dysproteinemia, have been observed in patients with both localized and disseminated tuberculosis.[16] Of course, one must keep in mind that various malignant disorders can lead to opportunistic tuberculosis.

Hyponatremia is especially seen in patients with tuberculous meningitis, felt to be related to inappropriate antidiuretic hormone (ADH) secretion. Since many of our patients consume alcohol heavily, the removal of alcohol while in hospital may also affect neurohypophyseal function.[7]

Certain chemical studies of body fluids can yield important information. As noted in this study, the order of frequency of involvement of body fluids is sputum first, cerebrospinal fluid second and other fluids third. The fluids are exudates with protein content greater than 3 grams per 100 ml, and high specific gravity. Cell counts can vary from several hundred to several thousand, with the predominant cell type being the lymphocyte. Low glucose and chloride levels are suggestive but not pathognomonic of tuberculosis. These findings are not always reliable and can also be present in cryptococcal and coccidioidal infections,[17,18] as well as in noninfectious conditions, such as rheumatoid arthritis.[19] However, true values are obtained only when pleural fluid and peripheral blood are taken simultaneously from fasting patients.[20]

The most useful approach is to obtain cultures of all body fluids and tissues that are suspected of being involved with M. tuberculosis.

It was unusual that antemortem liver biopsies were not carried out, for the liver is commonly involved in disseminated tuberculosis, as shown by the autopsy findings reported here. However, one must remember that noncaseating hepatic granulomata may also be associated with sarcoidosis, syphilis, brucellosis, histoplasmosis, berylliosis, Hodgkin disease, erythema nodosum and, ironically, some cases of intrathoracic tuberculosis.[8] Bone marrow, lymph node and skin lesions are other important sources of biopsy and culture. The finding of acid-fast bacilli in granulomatous

tissue obtained from biopsies is highly suggestive of, but by no means definitive evidence for, M. tuberculosis, since it is difficult to differentiate it from microscopic characteristics of other mycobacterial organisms or even mycobacteria-like organisms, such as Nocardia. Obviously, the culture clinches the diagnosis.

Any or all of the clinical, chemical and pathologic features described above can be seen in disseminated or miliary tuberculosis. This form of tuberculosis can mimic many other diseases. Many of the patients who died in this series presented in typical fashion. Symptoms preceded admission to the hospital by a few days to several weeks. Other workers have described symptoms preceding admission by several months.[7,8] Nonspecific and vague symptoms led patients to believe nothing was seriously wrong with them until it was nearly too late. Unless the physician has a high index of suspicion, he can also be misled. Three of five patients with disseminated tuberculosis died before a diagnosis could be made. In addition, in four of the five cases there was involvement of the central nervous system. Other workers have similarly found high mortality rates in cases associated with meningitis.[11]

The high incidence of meningitis occurring with miliary spread makes it mandatory that a spinal tap be done in every suspected case. Physical findings may be absent, and even spinal fluid findings may not be suggestive of tuberculosis. Unfortunately, even when one suspects tuberculous infection, all efforts to obtain bacilli from body fluids and tissue cultures may be fruitless. Weeks may be lost in "making the diagnosis." This has led many clinicians to treat now and diagnose later. It is possible to achieve this during the period following the initiation of therapy as tubercle bacilli can sometimes still be culturable during this period.

Extrapulmonary tuberculosis remains a persistent problem in today's population, concentrated at both ends of the age spectrum. The successful control of pyogenic infections has resulted in a rise of a new group of degenerative disorders that contribute to this persistence. It behooves physicians to be on the lookout for telltale localized or constitutional signs and symptoms. Early suspicion of extrapulmonary tuberculosis on this basis can lead to successful diagnosis and therapy.

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Unrecognized Causes of Platelet Transfusion Failure in the Presence of Anti-HL-A Antibodies

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When in a patient who is receiving random donor platelet infusions there is an inadequate rise in platelet count and anti-human HL-A antibodies are noted in the serum, it is natural to assume that platelet destruction results from an immunologic cause. Nonimmunologic causes of such failure do occur, however. Two of the most common are disseminated intravascular coagulation and splenomegaly.

PLATELET TRANSFUSION has by now become well established as a means of treatment of thrombocytopenias of depressed platelet production, whether due to leukemia, aplastic anemia or chemotherapy of malignant disease. Whether harvested from the blood of random donors or obtained by plateletpheresis of selected donors, about 65 to 70 percent of the infused platelets should circulate, many of the others being isolated in the spleen. Maximum survival of transfused platelets should normally be eight to ten days.[1]

It has also been established that platelets contain human leukocyte antigen (HL-A) and other hereditary antigens. In a large percentage of patients receiving many transfusions of random donor platelets, sooner or later anti-HL-A antibodies will develop which destroy transfused platelets unless they are of compatible HL-A type. So when the response in a patient who is receiving random donor platelet infusions consists of an inadequate rise in platelet count, and anti-HL-A antibodies are shown in the serum, it is natural to assume that platelet destruction is occurring because of an immunologic cause.

There are nonimmunologic causes of failure of platelet transfusion, however; two of the more common of these are disseminated intravascular coagulation (DIC) and splenomegaly with splenic sequestration. When either of these events occurs in a patient in whom the presence of anti-HL-A antibodies can be shown, it is very easy to overlook the complicating event, and assume that platelet destruction is due to the HL-A antibodies.

In a recent and continuing study by the National Institutes of Health of patients who had received many platelet transfusions, and who had become resistant to random donor platelets, the author encountered several with such unexpected complications. The following two cases serve as characteristic examples.

Reports of Cases

CASE 1. A 35-year-old Mexican-American woman entered the hospital on February 27, 1975, with a diagnosis of chronic granulocytic leukemia in "blast crisis." Chronic granulocytic leukemia had been diagnosed three years before because of a massively enlarged spleen and characteristic

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ABBREVIATIONS USED IN TEXT

ACT = activated coagulation time
APTT = activated partial thromboplastin time
CGL = chronic granulocytic leukemia
DIC = disseminated intravascular coagulation
Factor II = prothrombin
Factor V = proaccelerin
Factor VIII = anti-hemophilic globulin
FDP = fibrin degradation products
HL-A = human leukocyte antigen
PT = prothrombin time
TT = thrombin time

blood and bone marrow features. A Philadelphia chromosome (Ph') and partial deletion of chromosome G were also noted. Treatment had been carried out with hydroxyurea, busulfan and allopurinol, and in about 3½ months a complete remission had been achieved, which had been maintained fairly well until very recently without maintenance therapy. A rising leukocyte count with increasing numbers of myeloblasts prompted readmission of the patient to hospital.

On physical examination at admission, pallor of the skin was noted. The spleen was palpable 5 cm and the liver 4 cm below the costal margins. The patient reported that her right arm was sore and weak. An infiltrative lesion on the tongue, felt to be leukemic, was noted. The leukocyte count was 79,000 per cu mm, with a large percentage of myeloblasts and promyelocytes; the hematocrit was 23.5 percent; platelets numbered 74,000 per cu mm. The bone marrow was intensely hypercellular with myeloblasts and promyelocytes predominating. There were considerable numbers of megakaryocytes, however.

Treatment with radiation to spleen and tongue, and intensive therapy with hydroxyurea was carried out. There was no response; the spleen increased in size and the myeloblast count rose. An attempt was made to determine the patient's HL-A type, without success, so when the falling platelet count reached a hazardous level, two platelet infusions were given, each of four units from two available half-siblings. There was essentially no rise in her platelet count. She was then given 10 units of platelets from random donors, again without significant rise in the count. At this time, the presence of HL-A antibodies was shown by positive lymphocytotoxicity tests against eight of a panel of ten donor lymphocytes.

Eventually HL-A typing was successfully done and the patient was found to be type HL-A 1, 9; W-5, W-22, and group O. No donors of this type could be found in the local panel of close to 2,500 HL-A typed donors, so we chose a group A donor of type HL-A 1, 9; 7, W-10, the first two antigens being in common with those of the patient, the latter two being "cross-reactors" with the patient's antigen W-22. Four units of this donor's platelets raised the platelet count 4,400 per cu mm per unit, when corrected for the patient's surface area—a fairly satisfactory response, but by the next morning only 400 per cu mm survived in the circulation.

At this point it was decided that, although it was risky, the only hope of prolonging this patient's life significantly was by splenectomy, possibly to be followed by more hydroxyurea. Since we were unable to obtain even reasonably matched platelets with which to prepare the patient for surgery, the procedure was undertaken without previous platelet transfusion. However, as soon as the splenic artery was ligated, 15 units of group O random donor platelets were rapidly infused. The blood loss, which had been troublesome during the first stages of the operative procedure, almost immediately ceased and gave no more trouble subsequently. The striking rise in the platelet count, from 17,000 preoperatively to 185,000 postoperatively, is shown in Figure 1. Although fluctuating considerably subsequently, the count never again fell into bleeding levels. The patient died one week postoperatively in spite of postoperative hydroxyurea. Results of postmortem examination confirmed widespread infiltration with myeloblasts, but no recent abnormal bleeding.

CASE 2. A 55-year-old man was admitted to hospital with acute myeloblastic leukemia. On physical examination no massive splenomegaly or hepatomegaly was noted. Findings on laboratory studies showed progressive normoblastic anemia and grossly elevated leukocyte count, most of the cells being myeloblasts.

Under intensive chemotherapy with cytosine arabinoside and thioguanine, the leukocyte count fell to 1,500 per cu mm, with no myeloblasts, and the platelet count fell to 5,000 per cu mm, the bone marrow becoming extremely hypocellular. Transfusions of packed red cells supported the falling hemoglobin, and many units of random donor platelets supported the platelet count. Remission eventually occurred, and the patient left the hospital.

He returned for consolidation therapy, and there was no response to transfusions of random donor platelets. Antibody tests showed that a broad spectrum of anti-HL-A antibodies had developed. HL-A typing showed the patient to be to be HL-A 2, 10; W-5, W-16. We fortunately had in our file a donor of the same blood group and HL-A type, and four units of this donor's platelets caused a very significant rise in the patient's platelet count (Figure 2). He again left the hospital with moderate neutropenia and thrombopenia, but in early remission.

He returned seven months later, in a septic condition and with an extremely low platelet count. Hemostatic studies showed a fibrinogen of 250 mg per 100 ml (normal: 200 to 400), and an activated partial thromboplastin time (APTT) of 19.9 seconds (control: 33.9 seconds). Appropriate antibiotics were given, and 4 more units of platelets from the same HL-A identical donor. The platelet infusion this time caused a very small increment, but the patient responded to treatment of sepsis, and was again discharged.

He returned three months later, again in a septic condition and in relapse of the acute leukemia. Persistent epistaxis and a platelet count of only 7,000 per cu mm were noted. This time, the response to infusion of 4 units of platelets from the same HL-A matched donor was negative, the platelet count 20 hours after infusion having fallen from 7,000 to 2,000 per cu mm. Suspecting DIC due to sepsis, we initiated coagulation studies, but prothrombin time (PT) and thrombin time (TT) proved to be normal, and quantitative fibrinogen 275 mg per 100 ml. Fibrin degradation products ranged from 10 to 40 μg per ml—not considered a diagnostic level. The only abnormal finding on a hemostatic test, other than the platelet count, was the activated partial thromboplastin time of 22.5 seconds (control: 33.2 seconds).

In spite of the far from classical features of DIC, the clinician in charge agreed to light administration of heparin, feeling that in this preterminal patient, the survival of matched platelets might be significantly improved if the apparent DIC could be controlled. The patient therefore received 2,500 units of heparin, or about 35 units per kg of body weight, each four hours (15,000 units, or 210 units per kg of body weight per 24 hours). Three days after the previous platelet infusion, and two days after the start of heparin therapy, he again received four units of platelets from the same HL-A identical donor. The sepsis had remained essentially unchanged, but following the platelet infusion the nasal blood loss stopped and the platelet count rose from 3,000 to 14,000 per cu mm, and in the subsequent two days of heparin administration, to 28,000 per cu mm. The sepsis proved unmanageable, however, and the patient died a few days later, without active blood loss.

Discussion

In Case 1, although the HL-A antibodies undoubtedly were of importance, the rate of platelet destruction was tremendously hastened by the huge spleen, as shown by the increased survival after its removal. It is possible that the spleen had been producing a significant portion of the HL-A antibodies, as well as being the site of sequestration and destruction of most of the antibody-

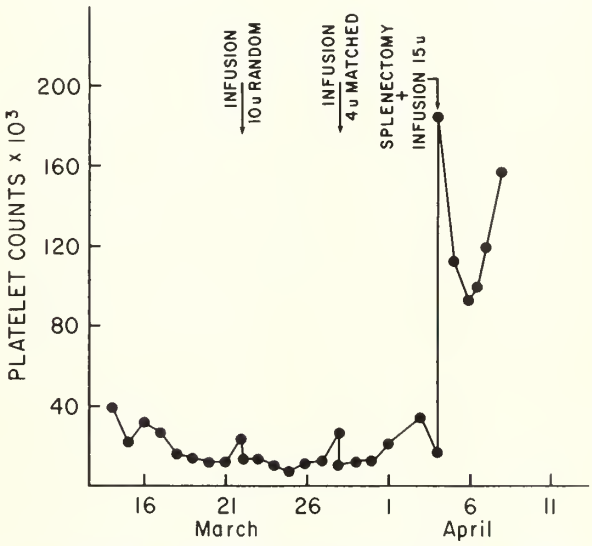

Figure 1.—Splenomegaly and survival of transfused random donor platelets in presence of anti-HL-A antibodies.

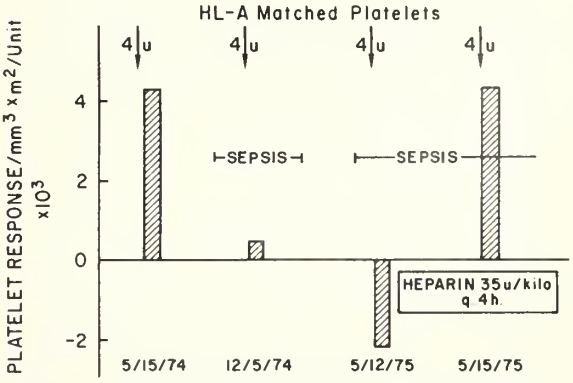

Figure 2.—Disseminated intravascular coagulation in terminal leukemia: Treatment with heparin and HL-A matched platelets.

injured platelets, because at examination it was found that considerable numbers of lymphocytes persisted in the spleen.

Although splenectomy of patients with massive spleens has long been known as a successful means of correcting thrombocytopenia due to hypersplenism,[2] we have found no reference in the literature to splenectomy in persons with a broad spectrum of anti-HL-A antibodies. Perhaps when faced with a patient with depressed thrombopoiesis, anti-HL-A antibodies and an absence of matched donors, one should not give up too readily. If the spleen is enlarged, its removal may allow additional time in which to explore further therapeutic methods.

The second patient presented a very different problem. The characteristic laboratory features of DIC, as widely recognized in recent years, include a decrease of those coagulation factors that are consumed in the production of a clot. The patient's blood may prove entirely incoagulable, due to a complete absence of fibrinogen, and assay findings show sharp decreases in factors VIII (antihemophilic globulin), II (prothrombin) and V (proaccelerin), as well as platelets. If the blood is not incoagulable, one characteristically encounters pronounced prolongation of the activated coagulation time (ACT), as well as the APTT, the PT and the TT. In addition, one finds strongly positive tests for fibrin monomers and fibrin degradation products (FDP). If fibrinogen survival studies are available, fibrinogen survival is found to be shortened. Thomas,[3] in a study of 58 patients with leukemia, found that 36 of them (62 percent) had episodes of blood loss associated with lowered fibrinogen and factor V, as well as platelets.

Gralnick and co-workers,[4,5] however, as well as Salvatori and co-workers[6] have reported that the laboratory features of DIC may differ sharply in patients with acute promyelocytic leukemia. They found APTT often abnormally *shortened,* the levels of fibrinogen and factor VIII varying from low to high, in spite of shortened fibrinogen survival. The PT and TT were usually normal, and fibrin monomer and FDP tests were not strongly positive. At times, the diagnosis of DIC proved very difficult to establish, but such patients, who had responded very poorly to platelet transfusions, showed normal increments when therapy with heparin was carried out before they received the platelets. Gralnick and Tan[5] suggested that such changes, although most characteristic of promyelocytic leukemia, occurred "more modestly" in patients with other forms of acute leukemia.

The patient in case 2 well illustrates the thesis of Gralnick and associates[4,5] that when platelet production is depressed, the laboratory picture of DIC may be very atypical. The patient's fibrinogen level was within usually accepted normal limits, although low for his physiologic state, since acute leukemias, particularly those with sepsis, tend to have abnormally high fibrinogen levels. Further, the APTT proved notably shortened on two occasions, as reported by Gralnick and Tan[5] in many of their patients. It is evident that when one encounters an undiagnosed thrombocytopenia, an APTT as well as fibrinogen level determination should be added to the panel of tests. If the fibrinogen level is decreased and the APTT prolonged, there is clear evidence of DIC. Likewise, if the APTT is abnormally shortened, as in this case, the evidence for DIC is strong, regardless of the fibrinogen level.

The most striking proof that failure of platelet infusions in this patient, in spite of the anti-HL-A antibodies, was not due entirely to isoimmunization was the fact that when he received HL-A identical platelets, they were destroyed rapidly. However, another similar infusion, given after heparin therapy had been carried out, caused a very satisfactory *rise* in the platelet count. The only possible explanation of this sharp change on low-dose administration of heparin is the assumption that the patient indeed had DIC.

One must remember, of course, that heparin therapy in a patient with severe thrombocytopenia involves appreciable hazard, and must not be undertaken lightly. On the other hand, platelet infusion in the face of DIC without heparin control is usually worthless. Judging by the results of the previous infusion in this patient, further infusion of matched platelets without control of the DIC would have proven valueless.

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Refer to: Embury SH, Elias L, Heller PH, et al: Remission maintenance therapy in acute myelogenous leukemia. West J Med 126:267-272, Apr 1977

Remission Maintenance Therapy in Acute Myelogenous Leukemia

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Because no conclusive evidence as to the efficacy of maintenance chemotherapy in acute myelogenous leukemia (AML) existed, a study to obtain such information was done. Twenty-six adult patients with AML in whom complete remission had been achieved following induction chemotherapy were randomly assigned to receive either maintenance chemotherapy consisting of cytarabine and 6-thioguanine for two days each month or to receive no maintenance therapy. The data showed a significant difference in remission duration between the two groups, with median remission lengths for the maintained and unmaintained groups being 10.3 and 6.7 months, respectively ($p<.05$). In 46 percent of the maintained patients there were remissions lasting longer than 11 months, whereas in none of the unmaintained patients was there such a prolonged remission. No significant drug-induced toxicity was observed. That the prolonged exposure to these chemotherapeutic agents, which were also used in our induction program, did not adversely affect the rate of successful reinduction therapy was shown by identical 50 percent complete remission rates for second inductions in both groups. In patients with palpable splenomegaly at the time of diagnosis, there was no prolongation of remission with maintenance therapy. These data indicate the potential utility of maintenance chemotherapy for prolonging remission duration in acute myelogenous leukemia.

DESPITE a lack of conclusive evidence, it has been assumed that maintenance chemotherapy is useful in the management of acute myelogenous leukemia (AML). This assumption is related to the established effectiveness of such therapy in acute lymphocytic leukemia.[1,2] However, the single controlled study suggesting efficacy of maintenance therapy in AML[3] had an exceedingly brief remission duration in the unmaintained group and failed to show this advantage when the dose of the chemotherapeutic agent, cytarabine, was increased. Other controlled studies of AML maintenance therapy[4] failed to show an advantage of mercaptopurine or of combination therapy with vincristine, methotrexate, mercaptopurine and prednisone compared with no maintenance therapy. Owing to a lack of concurrently unmaintained controls in recent studies,[5-7] it has

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ABBREVIATION USED IN TEXT
AML = acute myelogenous leukemia

been difficult to determine if the improved results have been the result of heavy maintenance therapy or modern induction programs. Recent reports on maintenance immunotherapy and chemotherapy lack untreated control groups and do not show a pronounced advantage of this type of treatment compared with chemotherapy alone.[8]

In order to determine if the implied theoretical advantage of maintenance therapy[9] outweighed the risk of its toxicity, we carried out a study comparing maintenance chemotherapy with no maintenance therapy in patients with AML in complete remission. When complete remission was documented, patients received a course of consolidation therapy which consisted of cytarabine and 6-thioguanine given over two days. The group receiving maintenance therapy received monthly treatment identical to consolidation therapy, while the other group received no further chemotherapy.

Materials and Methods

Patient Group

The patients in the study of maintenance therapy included 22 adults with AML (acute myeloblastic, monocytic or myelomonocytic leukemia), two with promyelocytic leukemia and two who had subacute myelogenous leukemia before conversion to classical AML. Patients had received no previous therapy for AML and there had been complete remission with standardized induction regimens supervised by the Stanford University Hematology Division. The median age of patients entered on the study was 45 years, with a range of 18 to 72 years.

Remission Induction Regimen

The induction program was modified from the programs of Clarkson, Gee and colleagues[6,7,10] by the addition of daunarubicin. With minor modifications therapy was administered as follows: daunarubicin, 60 mg per sq meter by rapid intravenous infusion, was given on the first day. This was followed in 12 hours by cytarabine, 3 mg per kg of body weight by rapid intravenous infusion, and 6-thioguanine, 2.5 mg per kg of body weight given orally. Administration of the last two agents was continued every 12 hours until biopsy-proven marrow hypoplasia was achieved. A second dose of daunarubicin between days 7 and 10 was nearly always given, the dose varying, depending on the cellularity of a marrow biopsy specimen. Changes in therapy from the original program[10] were undertaken so as to shorten the treatment program and decrease the time at risk from severe neutropenia and thrombopenia. That this was achieved is reflected in the shorter treatment period required to reach hypoplasia with the current drug program (15.4 ± 7.0 days, mean ± SD) compared with our earlier regimen[11] employing only a single daily dose of cytarabine and 6-thioguanine (23.8 ± 12.3 days) ($p < .01$, Student's t test).

During induction, patients received general ward care and oral mycostatin fungal prophylaxis. The induction and support therapy was administered under general ward care by the Stanford University medical house staff. Combination antibiotics were administered for documented or suspected sepsis, and amphotericin B was used in patients with proven or suspected fungal infection. Prophylactic random donor platelet transfusions were given when the platelet count descended below 10,000 per cu mm. Patients showing no rise in platelet count following random donor platelet transfusion received, when possible, platelets from related donors in order to obtain at least partial histocompatibility. No patient in this study received granulocyte transfusion or barrier isolation.

The characteristics of this induction program are exemplified by the courses of the last 30 consecutive patients admitted to the induction protocol, which included 18 of the 26 patients evaluated in the maintenance study. In 19 patients (63 percent) complete remission was achieved and in 8 (27 percent) there was partial remission. The induction is characterized by a period of chemotherapy to hypoplasia of 15.4 ± 7 days (mean ± SD), a period from marrow hypoplasia to rising platelet or neutrophil counts of 12.3 ± 5.5 days, a neutropenic (absolute neutrophil count < 500 per cu mm) period of 26.3 ± 7.5 days, a thrombopenic (nontransfused platelet count < 10,000 cu mm) period of 23.6 ± 11.2 and an incidence of presumed and documented sepsis of 97 percent (one of 30 inductions was without sepsis). The median age of these last 30 patients is 50.5 years, with a range of 16 to 74 years.

Consolidation Therapy

Consolidation therapy was given at the time complete remission was documented, usually three to four weeks after sustained rise in either platelet or neutrophil count began. The criteria for complete and partial remission have been previously described.[12] Consolidation therapy consisted of four four-hour infusions of cytarabine, 75 mg per sq meter, given every 12 hours and two oral doses of 6-thioguanine, 2.5 mg per kg of body weight, given every 24 hours.

Maintenance Therapy

At the time of consolidation informed consent was obtained and patients were randomly assigned to a group to receive either a monthly course of maintenance therapy identical to the consolidation therapy or to a group to receive no maintenance therapy. Patients in both groups were evaluated identically, in that they were seen monthly for thorough clinical evaluation, including complete blood count, platelet count and tests of bone marrow aspirate. This study was approved by the Stanford Medical Center Human Experimentation Committee.

Analysis

Duration of complete remission was calculated from the time of consolidation and marrow documentation of complete remission to the time when clinical relapse occurred. In five patients who did not receive consolidation, remission was dated from the time of marrow documentation of complete remission. Survival was dated from time of diagnosis to death with the exception of the two patients with subacute myelogenous leukemia in whom survival was dated from the time of their conversion to classical AML.

Advice on statistical analysis was given by Dr. Rupert Miller and analyses were by the two-tailed modified Wilcoxon test,[13] unless otherwise specified.

Results

Thirteen patients were randomly assigned to each study group. There is a distinct advantage of the maintenance program used, as shown by the significantly longer duration of remission for patients in this group (Figure 1, Kaplan-Meyer Actuarial Plot) ($p<.05$). The median duration of remission for the maintained and nonmaintained groups were 10.3 and 6.7 months, respectively. Furthermore, there were significantly more long

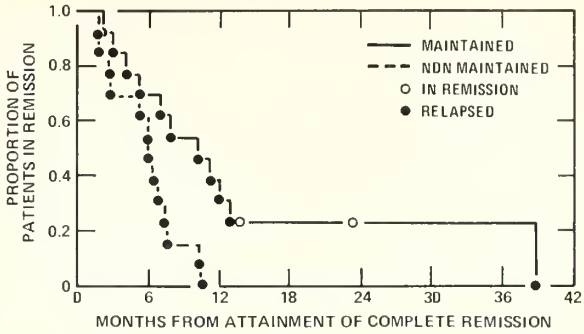

Figure 1.—Remission duration of patients randomly assigned to maintenance or no maintenance therapy.

remissions (defined as lasting at least 11 months following consolidation) in the maintained group as compared with the nonmaintained group, 46 percent versus 0 percent ($p<.05$, x^2 corrected) (Figure 1). Through various protocol misadventures, five patients in the group not receiving maintenance therapy failed to receive consolidation therapy. Comparison of this subgroup to the remainder of the nonmaintained group showed no difference in remission duration ($p>0.1$). Comparison of the consolidated patients in the maintained (13 patients) and nonmaintained (8 patients) groups indicated that the maintained group still had a significantly longer duration of remission ($p<.04$).

No drug-induced renal or hepatic toxicity or significant cytopenia was observed. Nausea and vomiting were seen only during the administration of chemotherapy, usually with the first infusion of cytarabine.

Since long remissions occur so infrequently in AML the incidence of long remissions was analyzed with respect to the following clinical features: age at presentation, sex, presence of splenomegaly, lymphadenopathy, leukocyte count, blast count, platelet count, fever, number of days of chemotherapy required to reach hypoplasia, doses of drugs required to reach hypoplasia, and number of days from documented hypoplasia to ascending platelet or neutrophil count. Our analysis showed that only presenting palpable splenomegaly was useful for predicting remission duration. In the maintained group, in which all long remissions occurred, the spleen was palpable in none of the six patients with long remissions, whereas in five of the nine patients with shorter remissions there were palpable spleens ($p<.05$). All nonmaintained patients had short remissions, six with palpable splenomegaly and seven without. Combining maintained and nonmaintained

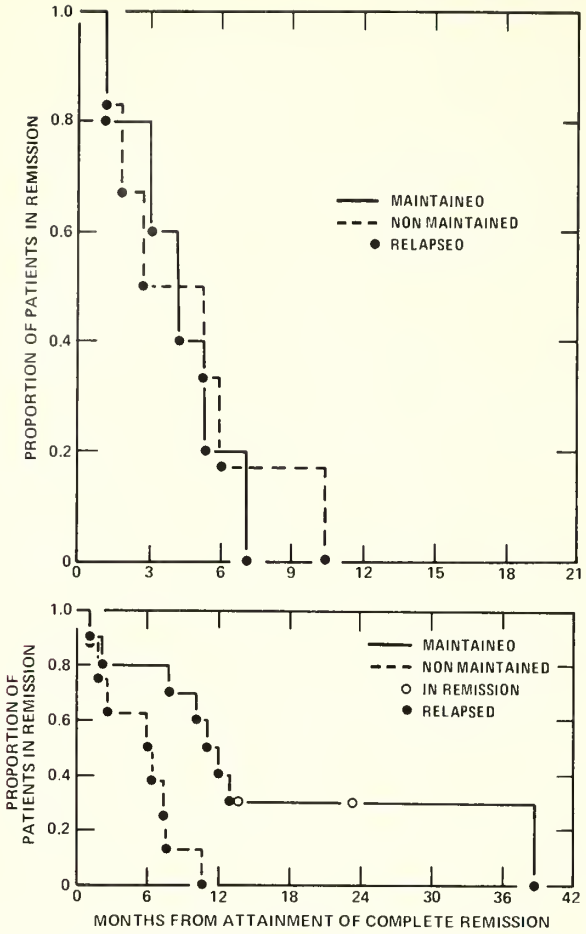

Figure 2.—Remission duration of the maintained and nonmaintained patients. **Upper,** with palpable splenomegaly at the time of diagnosis. **Lower,** without palpable splenomegaly at the time of diagnosis.

groups showed that palpable splenomegaly was of negative prognostic value for long remission ($p<.04$). The further significance of presenting splenomegaly is shown by analyzing the result of maintenance chemotherapy on remission length in the combined groups with and without splenomegaly (Figure 2). In those patients without splenomegaly there were longer remissions if maintenance therapy was given, whereas in those patients with splenomegaly remissions were short whether or not maintenance therapy was given ($p<.05$).

Analysis of the results of subsequent remission inductions with the same induction regimen according to whether or not the patient had received maintenance chemotherapy during the first remission showed no difference between the two groups. Of the eight previously maintained patients receiving a second course of induction, complete remission was achieved in four (50 percent), and of the

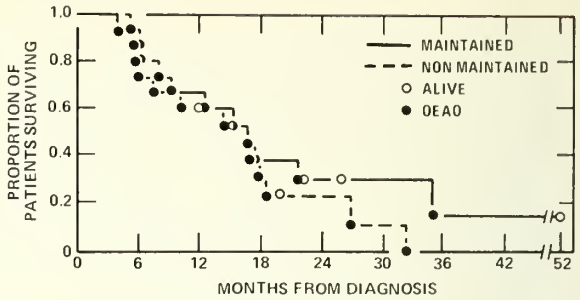

Figure 3.—Duration of survival of the patients receiving or not receiving maintenance therapy.

12 previously unmaintained patients receiving reinduction, there was complete remission in six (50 percent).

Four additional randomly assigned patients (two in each group), were not included in analysis of remission duration because they relapsed four to five weeks after consolidation, before the first maintenance course was due, and in this analysis their brief remissions would not have reflected differences in the two approaches. These four patients were, however, included in the analysis of survival where no difference was noted between the 15.4-month median survival of the maintained group and the 15.6-month median survival of the nonmaintained group ($p>.9$) (Figure 3).

Discussion

This study has shown that a nontoxic maintenance chemotherapy regimen prolongs the duration of remission in patients with AML. Median remission duration of maintained patients was 10.3 months, as compared with 6.7 months for patients receiving no maintenance therapy. Of the patients receiving maintenance therapy there were remissions lasting more than 11 months in 46 percent, as compared with no such long remission in the unmaintained group. Compared with a more intensive maintenance chemotherapy regimen,[6,7] this program entailed fewer days of therapy, was less myelotoxic and produced a comparable remission duration, but it yielded shorter overall survival. Although the cause for the shorter survival is unclear, the similar remission length implies that the difference lies not in the maintenance program, but in different results of salvage therapy following relapse. This difference may represent a variable severity of relapse which in turn may be a function of the intensity of earlier induction and consolidation therapies.

Current reports of long remission duration[5-8,14,15] employ both high dose maintenance therapy and modern induction programs, making it difficult to discern which modality is responsible for the improved results. A recent preliminary report showed no difference in remission duration or survival in comparing no maintenance therapy with high dose maintenance therapy.[16] Other comparative controlled data regarding the usefulness of maintenance therapy in AML are found only in studies conducted before the development of modern induction programs and fail to conclusively resolve the issue.[3,4]

The finding of significantly more remissions lasting longer than 11 months occurring in our group receiving maintenance therapy raises the possibility that such therapy may enhance the potential for prolonged remission. Although long remissions and survivals were occasionally seen in AML before modern therapy regimens,[17-21] an increasing incidence of such events[7,14] raises the possibility that certain programs are capable of achieving this effect. Further efficacy of postinduction therapy in remission prolongation has recently been reported using late intensification chemotherapy.[22]

The suspected efficacy of maintenance therapy is based not only on the advances seen in acute lymphocytic leukemia,[1,2] but also on several theoretical arguments. It has recently been shown that morphologically normal peripheral leukocytes from patients with AML in remission contain RNA-dependent DNA polymerase, the marker previously believed to have been specific for leukemic cells.[23] As the authors suggest, chemotherapy may be instrumental in the transition of the leukemic clone into a nonneoplastic clone which expresses only this viral function merely as a marker. A further theoretical consideration favoring maintenance therapy would argue from the kinetic viewpoint that the morphologically undetected leukemic cells persisting in remission have a high growth fraction concomitant with a reduced leukemic cell burden[9] and are thus more susceptible to cell cycle stage specific agents.[24] Assuming similar kinetics for leukemic and normal precursor cells, intermittent infusions were chosen because previous studies with several of our patients had shown that this type of therapy was capable of causing pronounced reduction in the number of granulocytic progenitor cells in DNA synthesis.[25]

We chose a maintenance program that was not significantly myelotoxic because there was no previous evidence showing efficacy of maintenance therapy. The program chosen required two days per month in hospital and permitted nearly normal activity, a goal which has been recently emphasized.[26] Furthermore, theoretical arguments could be advanced for a potential detrimental effect of chemotherapy on AML in remission if such therapy were to disturb a balance between emergent normal "feeder" stem cells and leukemic "sleeper" stem cells, postulated to exist during remission.[27]

Patients with palpable splenomegaly did not respond to maintenance chemotherapy with lengthened remission. However, in a study employing more intensive chemotherapy,[7] splenomegaly had been found to be of no prognostic significance. These contrasting observations, along with the suggestion that splenectomy during remission of childhood AML prolongs remission,[28] indicate that methods of reducing the splenic tumor burden to the point where it is no longer a determinant of remission length bear further investigation.

It has been shown that prolonged cytarabine therapy can induce elevation of cytidine deaminase levels concomitant with resistance to the drug.[29] The fact that reinduction with our DAT program following initial relapse produced identical remission rates in those who had received maintenance therapy and those who had not, indicated that the maintenance regimen does not uniformly induce clinically significant drug resistance.

In this study, the efficacy of maintenance therapy was not reflected by increased survival. However, since the patients were not managed in a consistent manner following relapse (some patients even electing to undergo no further induction therapy), the effect of maintenance therapy on survival is difficult to evaluate in this study, and the data that can be evaluated end with the first relapse.

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Initial Screening in Patients with Blood in Stool

During a routine rectal examination, a positive stool guaiac is found. What procedures should be followed to discover the source of the bleeding?

I think the initial screening that we would do probably would be sigmoidoscopy followed by barium enema. Certainly lesions in the upper tract also bleed, certainly the teeth can bleed and the nose can bleed and give a positive stool guaiac. We start with a physical examination of the patient and evaluation, and then listen to symptomatic history. And if we don't have any symptomatic history and no potential lesions, then I think we probably would start from the bottom up and then work down from the top. And I think if there was no lesion on any of our screening tests and blood persists in the stool . . . then at that point, one might consider an endoscopic evaluation, be it colonoscopy or upper gastrointestinal endoscopy.

We're engaged in a program of trying to evaluate just this problem. And our procedure is . . . a physical examination, protoscopy barium enema and flexible colonoscopy. We've had an extremely low incidence of false positives. We found significant pathology in just about everybody who had a repeat positive Hemoccult® slide. And strangely, very few of these cases were diverticular disease; most of them were polyps or cancer, or both.

—MAUS W. STEARNS, JR, MD, *New York, NY*
HARVEY W. OLSEN, *San Francisco*
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Specialty Conference

Moderator

JAMES H. MEYER, MD

Participants

ARTHUR SCHWABE, MD
JON I. ISENBERG, MD
RICHARD A. L. STURDEVANT, MD, MPH
MORTON I. GROSSMAN, MD, PhD
EDWARD PASSARO, JR., MD

This symposium was held April 28, 1976 at the Sepulveda Veterans Administration Hospital.

Refer to: Meyer JH, Schwabe A, Isenberg JI, et al: Treatment of peptic ulcer disease—A symposium, University of California, Los Angeles, School of Medicine and Sepulveda Veterans Administration Hospital (Specialty Conference). West J Med 126:273-287, Apr 1977

Treatment of Peptic Ulcer Disease — A Symposium

JAMES H. MEYER, MD:* Peptic ulcer disease remains an important source of morbidity and absenteeism and, consequently, economic loss to our society. The causes of ulcer disease are unclear, but diseases with poorly understood causes can be effectively treated on an empiric basis. We are here today to assess current treatment of ulcer disease.

To begin this discussion, Dr. Schwabe will describe conventional ulcer treatment. Dr. Isenberg will then try to assess for us the effectiveness of this therapy. Next, Dr. Sturdevant will summarize available information on promising, new pharmacotherapies. Dr. Grossman, Dr. Passaro and I will then discuss aspects of surgical treatment of ulcer disease.

ARTHUR SCHWABE, MD:† Factors implicated in the development of peptic ulceration are excessive and prolonged secretion of acid and pepsin and impaired mucosal resistance. Conventional ulcer therapy is designed to reduce the amount of acid in the stomach by neutralization, buffering or inhibition of secretion. The goals of this therapy are (1) to alleviate ulcer symptoms, (2) to promote ulcer healing and (3) to prevent complications and recurrence. To accomplish these goals antacids, anticholinergics and specialized diets are commonly used.

Antacids

Antacids have achieved wide acceptance by both patients and doctors as the single most effective and rational form of ulcer therapy. More than $100 million is spent each year in the United States for the purchase of antacids. Most patients with pain from an acute ulcer obtain prompt relief from 30 ml of liquid antacid, equivalent to about 60 mEq of neutralizing capacity.[1] However, scientific proof of antacid efficacy in achieving the goals of ulcer therapy is incomplete.

Increasing awareness of the pharmacology of antacids has led to the concept of tailoring the antacid to a patient's requirements and tastes.[1,2] Factors such as buffering capacity and duration of action determine dosage schedules. Relative cost, palatability, sodium content and side effects additionally are considered in the selection of one of many available antacid preparations for a given patient.

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ABBREVIATIONS USED IN TEXT
dm E_2 = 16, 16-dimethyl prostaglandin E_2
TDB = tri-potassium di-citrato bismuthate

The buffering effect of antacids in the fasting state lasts approximately 30 minutes. However, following a meal this buffering effect is prolonged to three to four hours. Liquid antacids are more effective buffers than antacid tablets. Although potent buffers, calcium-containing antacids increase gastric secretion after their buffering effect has subsided[3,4] and may also produce elevations in serum calcium, creatinine, phosphorus and bicarbonate. For these reasons, calcium-containing antacids cannot be recommended for ulcer management.

The above considerations underlie what we prescribe for patients with gastric or duodenal ulcer (Table 1), which is not far different from what most gastroenterologists advise.

Anticholinergics

The use of anticholinergics in the management of peptic ulcer is based on the observations that they reduce basal, nocturnal and stimulated gastric acid secretion. They may also prolong the duration of antacid action by keeping antacid in the stomach longer.

The desired antisecretory effects of anticholinergics are invariably accompanied by predictable side effects, such as dry mouth and constipation. When a decision is made to use one of these agents, the dose has to be titrated to a level just below that which produces these side effects. The optimum effective dose varies with each individual patient, with the type of preparation and with the time of administration. The duration of action of these drugs is greatest when taken after a meal. Absolute and relative contraindications of anticholinergics are listed in Table 2.

Because of the narrow margin between desired and untoward effects and occasional severe complications, anticholinergics have lost much of their popularity in standard ulcer therapy. They are most effective if given at bedtime for reduction of nocturnal acid secretion and nighttime pain.

TABLE 2.—*Anticholinergics in Treatment of Peptic Ulcer*

Absolute Contraindications
Gastric retention
Glaucoma
Prostatism
Pulmonary disease (chronic)
Relative Contraindications
Constipation
Central nervous system symptoms
Esophageal reflux
Impotence
Hot climates (anhidrosis)
Old age

Diet

A bland or restrictive diet has traditionally been an accepted component of conventional ulcer therapy. The precise composition, caloric content and number of feedings of these ulcer diets vary. In some of these diets it is presumed that dark meat, dark bread, spices, raw fruits and uncooked vegetables aggravate or perpetuate an ulcer and are therefore contraindicated. Consequently the use of milk, cottage cheese, white fowl meat, rice, mashed potatoes and vegetables prepared in a blender is stressed. Although as a rule these diets are monotonous and unpalatable, most patients readily accept, or may even request, dietary restrictions.

A brief review of our current knowledge of the physiologic effect of the different dietary constituents on gastric secretion is in order. A standard meal has been shown to neutralize gastric contents for 30 to 60 minutes and is then followed by increased acid secretion and an increase in gastric acidity.[5] Constituents of foods vary in their buffering capacity and in their ability to stimulate acid secretion. The immediate effect of food protein is to buffer gastric acid, but this is followed by active stimulation of gastric secretion. The net

TABLE 1.—*Guidelines for Antacid Therapy*

Type: Mixtures of aluminum hydroxide; magnesium hydroxide; magnesium trisilicate

	Dosage	*Frequency*	*Maintenance Rx*
Gastric Ulcer	40 mEq (15-20 ml)	Every hour for 12 weeks*	1-3 hours after meals and on retiring; indefinitely†
Duodenal Ulcer	75-100 mEq (30-60 ml)	Every hour for 2 weeks	1-3 hours after meals and on retiring; for 6 weeks

*Ulcer must show signs of healing after 3 weeks.
†If ulcer has completely healed.

effect of a protein meal is to increase the load of acid delivered to the duodenum. Although fats and carbohydrates cause less stimulation of acid secretion, they have little or no buffering capacity. Fruit juices contain a significant amount of buffer and tend to maintain a pH near their own level. Pepper in the absence of food may produce gastric hyperemia and edema, but there is no evidence that it causes peptic ulceration. Evidence that other spices cause peptic ulcer is nonexistent. Caffeinated beverages have been clearly shown to stimulate gastric secretion. Alcohol does not stimulate acid secretion, but may produce gastritis.

There is no evidence that a bland diet is of any benefit in ulcer management.[6] Other time-honored concepts, such as hourly administration of milk and cream, multiple feedings and the bedtime snack, have been shown to induce a net increase in the acid load and have been abandoned.

For patients with peptic ulcer, there should be dietary restrictions on alcohol, caffein-containing beverages and aspirin. Finally, patients should be encouraged to eat three nutritious, enjoyable meals of their own choosing every day.

JON I. ISENBERG, MD:* Does conventional ulcer therapy, as outlined by Dr. Schwabe, really work? Probably not, but we really do not know. The reasons for this uncertainty are related to the following factors which make therapeutic studies in peptic ulcer difficult. First, ulcer disease waxes and wanes spontaneously. Therefore, a spontaneous cure may be confused with a therapeutic cure. Consequently, only large and carefully controlled studies can show therapeutic efficacy. Second, only recently have studies been directed at determining the natural history of ulcer disease using endoscopy to quantitate healing rate. Most of the earlier studies used x-ray examination, which is notoriously inaccurate in quantitating the size of duodenal ulcers. Third, as is the case with many clinical studies, criticisms can be made regarding experimental design. Factors such as double-blindedness, randomization, use of a satisfactory placebo and the like were often not taken into account in many of the earlier studies.

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Antacids

The mainstay of ulcer therapy over the past 20 centuries has been antacids. Pliny in the first century AD was reported to have used crushed coral, chalk, to relieve abdominal pain. Paracelsus, in the 16th century, used powdered pearls, somewhat more costly than antacids. Others followed suit with minor variations on the theme; Rokitansky adding milk and alkaline powders. With such a strong tradition, it is difficult to question the role of antacids in ulcer therapy. Also, the use of antacids seems to make good sense: (1) ulcers do not form in the absence of acid and antacids reduce both acidity and peptic activity, (2) antacids prevent the formation of experimental ulcers in animals and (3) surgical therapy, which usually cures ulcers, is thought to produce its effect by decreasing acid and pepsinogen secretion.

Now let us examine the effectiveness of antacids. We need to know (1) whether antacids

TABLE 3.—*Effects of Antacids or Placebos on Ulcer Pain*

		Blind	Test Agent	Ulcer	Results
Placebo alone					
1936	Flood and Mullins[6]	o	Histidine vs saline	DU	8/12 saline relief, 4/6 hist. relief,
1947	Gill[7]	o	Sterile water	GU	19/20 relief
Antacid vs Placebos					
1947	Smith[8]	o	Reactive vs non-reactive aluminum hydroxide	DU	No difference in 63 patients
1952	Lawrence[9]	o	Barium vs aluminum hydroxide, magnesium carbonate, magnesium trisilicate	DU, GU	Magnesium better than barium or aluminum
1973	Hollander, Harlan[11]	+	Calcium carbonate vs placebo tablet	DU, GU	No difference DU, AA effect in GU
1975	Butler, Gersh[12]	+	Aluminum + magnesium AA vs placebo	GU	No difference
1976	Sturdevant et al[13]	+	Aluminum + magnesium AA vs placebo	GU	No difference

o indicates nonblinded study
+ indicates double-blind
DU indicates duodenal ulcer
GU indicates gastric ulcer
AA indicates antacid

relieve ulcer pain (Table 3) and (2) whether antacids promote ulcer healing (Table 4) as compared with inactive, placebo agents.

In 1936, Flood and Mullins[6] reported that daily parenteral injections of saline produced relief in 8 of 12 symptomatic outpatients with duodenal ulcers within a few days. Gill[7] in 1947 reported that injection of distilled water resulted in pain relief in 19 of 20 patients with gastric ulcers and that ulcer healing occurred over four to eight weeks as determined gastroscopically. Both studies failed to contrast the responses to that produced by conventional therapy (this is, admission to hospital, changes in diet, use of antacids, cessation of smoking and so forth), but both studies suggested that ulcer pain is responsive to placebo effects.

Comparisons between inert placebos and antacids began in 1947 (Table 3). Smith[8] reported a reactive liquid aluminum hydroxide antacid tablet relieved pain no more effectively than a nonreactive aluminum hydroxide tablet which probably had little, if any, buffering effect. Lawrence[9] examined the effect of serial doses of liquid barium sulfate (placebo) with aluminum hydroxide and magnesium carbonate or magnesium trisilicate in 108 patients with either gastric or duodenal ulcers. The magnesium-containing antacids were superior to either barium or aluminum hydroxide in producing pain relief. Of the magnesium treated patients there was either partial or complete pain relief in 85 percent, while relief occurred in about 50 percent of the patients treated with barium sulfate and aluminum hydroxide. Palmer[10] reported that of 230 patients in hospital, 106 preferred aluminum hydroxide antacid, 93 preferred diluted hydrochloric acid and 31 had no particular preference as to which of the two agents produced greater relief of ulcer pain.

While these studies compared pain relief from antacids with that from placebos, they were not blind studies, and results were conflicting among the studies. Double-blind comparisons have been made only recently.

Three double-blind prospective studies have examined the effect of antacid versus placebo in relieving ulcer pain. Hollander and Harlan[11] contrasted the effect of calcium carbonate plus glycine tablets in both patients with gastric ulcers and those with duodenal ulcers. In the patients with gastric ulcers, antacid was found to be superior to placebo in relief of ulcer pain: all antacid-treated patients were pain-free after 30 days of treatment, while only 50 percent of the placebo-treated patients were pain-free. In the patients with duodenal ulcers, antacids tended to be superior to placebo in relief of ulcer symptoms, but the differences were not statistically significant. Butler and Gersh contrasted 30 ml of a liquid antacid with placebo in inpatients with gastric ulcers. They claim[12] that all of their patients were pain-free within 72 hours of admission to hospital. There were no distinct differences between those treated with antacid and those treated with placebo. Sturdevant and associates[13] have attempted to determine if single doses of antacid differ from placebo in relief of symptomatic duodenal ulcer pain. They conducted two studies; one with patients in hospital and the second largely with outpatients. The inpatients received serial doses of antacid or placebo for pain over five days and recorded their pain relief. The second group was carefully evaluated in five-minute intervals for 30 minutes after ingestion of antacid or placebo for two separate episodes of pain. There were no differences in time of onset of pain relief, duration of pain relief or degree of pain relief. *Taken together these results suggest that antacids are probably not notably different from a liquid placebo in relief of ulcer pain.*

Now to turn to the question "Do antacids expedite healing?" (Table 4). Sir Richard Doll and his associates at the Central Middlesex Hospital, London,[14] were the first group to evaluate carefully a number of treatment programs in ulcer patients. Their patients were randomly assigned to type of treatment, and in some cases a placebo was used, but the studies were not blind. Radiography was used as the measure of gastric ulcer healing. They studied a number of therapeutic approaches and agents simultaneously (such as ascorbic acid, phenobarbital, hospital admission, belladonna and sodium bicarbonate plus milk drip). They observed that a six pint per day milk drip plus 40 grams of sodium bicarbonate did not alter gastric ulcer healing when contrasted to a control group not receiving the milk drip.

Baume and Hunt[16] found that healing of gastric ulcers in outpatients was no different in those treated hourly with calcium carbonate powder when contrasted to those treated with an inactive aluminum hydroxide tablet over a three week period. In fact the mean decrease in ulcer size

at three weeks was less in those who received calcium carbonate (29 percent) than those who received the inactive aluminum preparation (56 percent).

Using endoscopy for measuring, Hollander and Harlan reported that in their antacid-treated gastric ulcer group there was more ulcer healing than in a placebo-treated group. However, Butler and Gersh[12] were not able to confirm these findings in 28 patients in hospital with gastric ulcers who were randomly assigned for liquid antacid or placebo administration. They observed that in 11 of 15 antacid-treated and in 10 of 13 placebo-treated patients there was at least 67 percent healing after three weeks in hospital.

In summary, antacids are probably no more effective than placebo in ulcer healing. Possible reasons for their lack of efficacy include poor patient compliance, transient buffering effect and factors other than acid or peptic activity which influence ulcer healing.

Should we continue to prescribe antacids for patients with ulcers? I think that we should because they are the current standard of practice. If additional studies fail to show a distinct efficacy, their future use may be curtailed.

Anticholinergics

Unfortunately, the story regarding the efficacy of anticholinergics is no clearer than the antacid tale. Although approximately $65 million is spent each year for anticholinergics, we remain uncertain that they are of proven efficacy in expediting ulcer healing, relieving pain or decreasing the frequency of complications or recurrences. The same difficulties are encountered in evaluating these agents as in evaluating the effectiveness of antacids. In addition, the anticholinergic saga is compounded by the difficulty of designing blind studies for testing the drugs because anticholinergics have inherent nongastrointestinal side effects (such as dryness of the mouth, blurred vision and urinary retention).

A large number of studies have been directed at determining whether anticholinergics are superior to placebo in the relief of ulcer recurrences or complications (Table 5). Those in which a fixed dose of anticholinergics has been used probably should not be given much weight, because it is well known that in order for anticholinergics to effectively inhibit acid secretion they should be prescribed at an individually determined optimal effective dose (that is, the dose one increment less than that which produces significant side effects).

Most (9 of 12) of the studies failed to document the effectiveness of anticholinergics in preventing ulcer recurrences and complications. Sun[21] and Sun and Ryan[22] claimed that there were fewer ulcer recurrences in patients with duodenal ulcers treated with anticholinergics when compared with a placebo-treated group, but complications occurred with almost equal frequency in the two groups. Amure's[23] results in patients with duodenal ulcers studied in Nigeria are difficult to evaluate because the superiority of anticholinergics versus placebo was related primarily to chronic vomiting in 97 percent of the placebo-treated groups, whereas, chronic vomiting is not frequently encountered among groups of ulcer patients in our society.

Three studies deserve brief comment. Walan[24] reported that there were significantly fewer recurrences and complications with less time lost from work over a two-year period in a group of 29 patients with duodenal ulcers treated with anticholinergics versus those receiving placebo. However, this was not a blind study and it is difficult to determine if biases might have influenced the findings. Baume and Hunt[25] reported greater gastric ulcer healing in inpatients and fewer gastric ulcer recurrences in outpatients treated with anti-

TABLE 4—*Effectiveness of Antacid on Ulcer Healing*

		Blind	*Test Agent*	*Ulcer*	*Results*
1956	Doll et al[15]	o	Multiple agents, milk + HCO_3	GU	No effect of milk + HCO_3 vs no treatment
1969	Baume, Hunt[16]	±	$CaCO_3$ vs inert AlOH tablet	GU	No difference in outpatient healing
1973	Hollander, Harlan[11]	+	$CaCO_3$ vs placebo tablet	GU	Effective in GU No effect in DU
1975	Butler, Gersh[12]	+	Aluminum + magnesium AA vs placebo	GU	No difference

o indicates unblinded
+ indicates double-blind
± indicates some degree of blindness but not truly double-blind

DU indicates duodenal ulcer
GU indicates gastric ulcer
AA indicates antacid

HCO_3 indicates bicarbonate
$CaCO_3$ indicates calcium carbonate
AlOH indicates aluminum hydroxide

cholinergics. Again, this was not a fully blind study and therefore its results are open to some question. Ruffin and Cayer[26] found that anticholinergic therapy was associated with fewer recurrences, fewer gastrointestinal hemorrhages and better clinical results than placebo in patients with duodenal ulcers treated for at least eight months.

It seems to me, *as with antacids, anticholinergics do not have a consistent therapeutic effect on peptic ulcer with respect to healing, recurrence or complications.* They may be of value, as they are often stated to be, in those patients with ulcers who have nocturnal pain, or in those who are recalcitrant to routine antacid therapy. However, their efficacy under these conditions needs to be carefully evaluated.

Finally, a brief comment on admission to hospital and discontinuation of smoking in patients with gastric ulcer. Doll and co-workers[14] reported that the healing of gastric ulcers in patients in hospital was greater than in outpatients; but these studies were confounded by the simultaneous prescription of other treatments while the patients were in hospital and therefore the conclusion must be qualified. Because the economic burden of three weeks of hospital stay is so great, most patients with gastric ulcers are admitted only for evaluation to be certain that the ulcer is benign, and then discharged. Since most gastric ulcers heal with outpatient management, this policy is certainly acceptable, provided the physician is finally able to ascertain complete healing during the course of outpatient management.

Also, Doll and associates[14] showed that discontinuation of cigarette smoking by patients produced faster gastric ulcer healing than occurred in patients whose smoking habit was unaltered. However, nonsmokers had slow rates of ulcer healing comparable to those in the continuing smokers, so the effects of abstinence from smoking were not totally clear. Moreover, Hermann and Piper[32] were not able to confirm these observations in a retrospective study; but since smoking is hazardous to one's health the use of tobacco should be curtailed.

Neither of the two major classes of drugs that have been extensively used, antacids and anticholinergics, appears to have a dramatic effect consistently and significantly greater than placebo. Clinical studies of the more potent acid-pepsin

TABLE 5—*Do Anticholinergics Really Work?*

		Number of Cases	*Blind*	*Test Agent*	*Ulcer*	*Results*
1954	Doll and Pygott[17]	32	o	Belladonna	GU	No difference, healing
1954	Friedlander[18]	100	o	Methantheline	DU	No difference, recurrence
1961	Melrose, Pinkerton[19]	58	+	Poldine methylsulfate*	DU	No difference, recurrence
1961	Lennard-Jones[20]	11	±	Poldine methylsulfate*	DU	No difference, recurrence
1964	Sun[21]	37	+	Glycopyrrolate (Robinul®)*	DU	Less recurrence in treated vs placebo, equal complications
1965	Amure[23]	120	+	Glycopyrrolate (Robinul®) Propantheline bromide (Pro-Banthine®)	DU	Anticholinergics superior
1966	Hunt, Wales[27]	13	+	Poldine methylsulfate	DU	No difference, recurrence
1967	Trevino, et al[28]	46	+	Glycopyrrolate (Robinul®)*	DU	No difference, recurrence
1968	Goyal, et al[29]	60	+	Oxyphencyclimine hydrochloride (Daricon®)	DU	No difference, recurrence
1970	Sun, Ryan[22]	75	+	Propantheline bromide (Pro-Banthine®)	DU	Less recurrence in treated vs placebo, equal complications
1970	Kaye, et al[30]	91	o	Propantheline bromide (Pro-Banthine®)* L-hyoscyamine sulfate	DU	No difference, recurrence
1970	Walan[24]	50	±	L-hyoscyamine sulfate*	DU	Less recurrence in treated
1971	Baume, et al[25]	40	±	Glycopyrrolate (Robinul®)*	GU	Greater healing in inpatient and less recurrence in treated
1972	Cocking[31]	65	o	Propantheline bromide (Pro-Banthine®)	DU	No difference, symptoms, recurrence

726 DU patients randomized
72 GU patients randomized

o indicates unblinded
+ indicates double-blind
± indicates some degree of blindness but not truly double-blind

DU indicates duodenal ulcer
GU indicates gastric ulcer

*Indicates optimal effective anticholinergic dose treated.

inhibitors (such as H_2-receptor antagonists, prostaglandins) and other agents (such as bismuth) may make important inroads toward improving ulcer therapy.

RICHARD STURDEVANT, MD:* Because the effectiveness of traditional ulcer therapy is in question, the search continues for more effective agents. Experimental drugs potentially useful in treatment of peptic ulcer include carbenoxolone; 16, 16 dimethyl prostaglandin D_2; cimetidine, and bismuth. None are available now for routine use in the United States.

Carbenoxolone is synthesized from glycyrrhetinic acid extracted from liquorice root. It nearly halves the time for healing of gastric ulcers in outpatients.[33,34] Its mechanism of action is not established. Its known effects on gastrointestinal physiology, which may be related to its ulcer healing effect, are listed in Table 6.

The recommended dose is 100 mg three times a day for one week, followed by 50 mg three times a day until the ulcer heals. The toxicity of carbenoxolone closely resembles that of excess aldosterone. With the recommended dose, about 50 percent of patients will have water retention or hypertension as side effects.[35,36] Hypokalemia is somewhat less frequent, but may be life-threatening.[37] Worsening of preexisting congestive heart failure results from sodium and water retention.

Side effects may be treated with a thiazide diuretic and potassium supplements. Antialdosterone drugs block not only the side effects, but also the therapeutic action of carbenoxolone.

Because of the side effects, structurally closely-related compounds have been tested. Of these, the most promising seems to be geranyl farnesyl acetate (Gefarnate®). This drug lacks carbenoxolone's side effects, but is less effective.[33]

Carbenoxolone is neither clearly effective in treatment of duodenal ulcers nor, when given chronically, in prevention of recurrence of gastric ulcer.

Prostaglandin E_2

16, 16-Dimethyl prostaglandin E_2 (dm E_2) is a synthetic prostaglandin which reduces gastric acid secretion when given by mouth. Some of its effects on gastrointestinal physiology are listed in Table 7. Its mechanism of inhibition of acid secretion is not established. While an effect via cyclic adenosine monophosphate (AMP) seems plausible, this has not been proven. Inhibition of acid secretion may be secondary to inhibition of gastric mucosal blood flow.[38]

TABLE 6.—*Effects of Carbenoxolone*

Increased life span of gastric epithelial cells
Increased volume of gastric mucus
Altered composition of gastric mucus
Inhibition of pepsin
Decreased back diffusion of hydrogen ion
Release of secretin into blood

TABLE 7.—*Some Gastrointestinal Effects of Prostaglandin E_2*

Decreases
Gastric acid secretion
Gastrin secretion
Gastric mucosal blood flow
Gastric emptying
Antral contraction
Colon contraction (circular muscle)
Increases
Hydrogen ion back-diffusion into gastric mucosa
Jejunal sodium and water secretion
Colon contraction (longitudinal muscle)

Dm E_2 increased the healing rate of gastric ulcers in one small trial in man.[39] No other therapeutic trials have been reported. In animals it inhibits the formation or hastens healing of ulcers or erosions in several experimental models. Dm E_2 may "break" the gastric mucosal barrier to acid back-diffusion.[40,41] Despite this observation, it is effective in rats in reducing the amount of gastric mucosal bleeding due to the "barrier-breakers"—aspirin, or aspirin and taurocholic acid together.[42]

Diarrhea occurs in some patients following administration of dm E_2 in doses for therapy.[39] The diarrhea is probably related to the secretory and motor effects of dm E_2 (Table 7).[43]

Cimetidine

Cimetidine is a synthetic compound structurally related to histamine.[44] It inhibits those effects of histamine not blocked by conventional antihistamine drugs (such as diphenhydramine). Histamine effects blocked by conventional antihistamines are thought to be mediated by H_1 receptors on cell membranes; effects blocked by cimetidine are mediated by H_2 receptors[44] (Table 8). This is analogous to the alpha and beta adrenergic blocking drugs.

A prominent H_2-mediated effect is gastric acid secretion. Cimetidine inhibits all the commonly

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TABLE 8.—*H_2-Receptor Mediated Histamine Effects*

Gastric acid secretion
Atrial contraction
Relaxation of the pregnant uterus
Inhibition of cytolysis by T lymphocytes
Arteriolar dilatation
? Intrinsic factor secretion
? Others to be discovered

tested stimulants of gastric acid secretion. In patients with duodenal ulcers, 400 mg four times a day produced a 67 percent reduction in mean 24-hour gastric acidity.[45]

Preliminary data, largely uncontrolled or unpublished as of April 1976, indicate that cimetidine or metiamide (another H_2-blocker) is effective in healing duodenal and gastric ulcer, and in stopping bleeding from "stress" ulceration.[46-48]

Side effects from cimetidine have not yet been reported. Metiamide produced small, but worrisome, increases in serum transaminases and creatinine levels in about 25 percent of patients with duodenal ulcers during four weeks of therapy.[46] Metiamide produced agranulocytosis in seven patients, with one death from subsequent sepsis in a patient with systemic mastocytosis.[49] The bone marrow toxicity is thought to be related to the thiourea moiety in metiamides's structure, rather than to an H_2-receptor effect, and thiourea is not present in cimetidine. Evidence supporting the thiourea as the cause of the agranulocytosis includes (1) thioureas are known to cause agranulocytosis; (2) in contrast to metiamide, no bone marrow depression occurred in chronic toxicity tests with cimetidine in animals; (3) one patient in whom agranulocytosis developed during metiamide therapy was switched to cimetidine, and the agranulocytosis disappeared.

The effects of long-term blockage of H_2-receptors are unknown (Table 8). Additional H_2-receptors may be discovered. These facts indicate the need for caution in undertaking chronic treatment with cimetidine.

Both cimetidine and dm E_2 are effective in notably reducing acid secretion in patients with Zollinger-Ellison syndrome. These drugs may be useful in chronic treatment of some of these patients.

Bismuth

Tri-potassium di-citrato bismuthate (TDB) is a colloidal bismuth compound under investigation abroad for ulcer treatment.[50] Its mechanism of action is uncertain; the current hypothesis is that the bismuth chelates with proteins in the ulcer base, somehow promoting healing.[50] The bismuth is apparently not absorbed from the gastrointestinal tract.[50]

Preliminary results are encouraging. Increased healing rate (judged by endoscopy) and symptom relief have been reported for both duodenal and gastric ulcer in controlled trials.[50] The drug has no known toxicity.

In summary, cimetidine is the experimental drug apparently closest to release for general use in ulcer therapy in the United States. While it will probably be found effective in healing ulcers, its toxicity remains to be determined. TDB seems more promising because its potential for toxicity appears to be less; however, it is not now under investigation in the United States. Carbenoxolone and dm E^2 are, in this reviewer's opinion, of limited potential value because of their side effects.

Cimetidine and perhaps dm E_2 may prove of value in treating Zollinger-Ellison syndrome. Cimetidine is now available for experimental use in this condition.

DR. MEYER: We have just heard that traditional medical therapy of ulcer disease is directed at reducing acidity. Such an approach, while intuitively rational, lacks proven effectiveness. More effective agents are therefore being sought and tested. However, an alternative to pharmacotherapy is surgical treatment of ulcer disease. In the second half of this symposium we will consider surgical therapy. Since most ulcer patients are operated upon because their disease is considered to have been refractory to medical treatment, Dr. Grossman will open the discussion of surgical treatment by trying to define intractability for us. Dr. Passaro will indicate for us what factors influence a surgeon in choosing a particular operation for an ulcer patient, and I will close the symposium with a discussion of the outcome of surgical treatment.

MORTON I. GROSSMAN, MD, PH D:* The dictionary defines intractability, in the medical sense, as "unresponsiveness to treatment." Use of the word implies that an effective treatment for the disease in question is available but that the treatment fails in a certain fraction of patients who are therefore said to have intractable disease. None of the conventional medical treatments of duodenal ulcer

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have been shown to be more effective than no treatment at all; yet, the term intractability is frequently applied to patients with this disease, particularly in relation to indications for surgical operation. More than half of the patients who receive elective surgical treatment for duodenal ulcer have intractability listed as the primary indication for the operation.

We are caught in a kind of semantic trap. Having adopted intractability as the major criterion for elective surgical operation in duodenal ulcer, we then proceed to justify this by stating the case in terms of response to therapy. Since we have no convincing evidence that medical treatment alters the short-term or long-term course of duodenal ulcer disease, we should not use response to such treatment as the major criterion for whether or not to offer surgical treatment to the patient.

For example, some current gastroenterology textbooks state the opinion that a patient with a duodenal ulcer must fail a test of medical treatment while in hospital before being offered the surgical option. During medical-surgical conferences at which elective surgical operation for duodenal ulcer is being discussed, remarks such as the following are frequently heard: "Although this patient has had severe symptoms from his ulcer for more than half the time during the past two years, he has never had a regimen of strict medical therapy during hospitalization and therefore should not be offered surgical therapy until this has been tried." I know of no evidence that the outcome of such a test of medical therapy has value in predicting the future course of the disease and I am therefore not inclined to place very much weight on it.

If intractability is not a valid criterion for selecting patients for surgical therapy, how should this decision be made? I believe that severity of the disease is the proper criterion. The question to be answered is the following: Is this patient's duodenal ulcer disease sufficiently severe to warrant taking the risks that accompany surgical treatment (death, recurrence, side effects of operation and dollar cost)? In weighing risks against benefits in this situation, the risks are relatively fixed and known but the possible benefits—namely, the degree of relief that may come from getting rid of the symptoms—is a function of the severity of those symptoms. So we try to answer another question: Are the symptoms in this patient sufficiently severe that the chance of abolishing them warrants the risks of the operation?

TABLE 9.—*Indices of Severity*

Frequency and intensity of pain
Special symptoms: Night pain, back pain, vomiting, etc.
Antacid consumption
Loss of time from work
Admissions to hospital
Complications: documented or suggested by symptoms

If, as I propose, severity is to replace intractability as an indication for elective surgical treatment in duodenal ulcer, we must develop and perfect quantitative indices of severity. Table 9 shows some of the items that might be used for this purpose. Frequency and intensity of pain are the prime indices. We are now beginning to learn how to record information about frequency and intensity of pain in a quantitative and reproducible fashion: During how many hours of the past day was your pain present? How many days of the past week? How many weeks of the past year? How many years of the past decade? Was the pain severe enough to interfere with your activities? Special symptoms such as night pain, back pain, vomiting and others should be separately recorded. Antacid consumption can be a useful index of severity and is readily quantitated. Loss of time from work is an important quantitative index of severity, as are numbers of admissions to hospital.

The complications of duodenal ulcer—including bleeding, impaired gastric emptying, perforation and penetration into adjacent organs—sometimes require emergency surgical procedures but if not they are then usually regarded as separate indications for elective surgical treatment. Ideally, we should combine all of these indices into a single quantitative assessment of severity. This, of course, requires a system of quantification and weighting that is not now available.

I believe three steps are needed to make the choice of surgical therapy more rational. First is improved nosology. We must define quite precisely what it is that we mean by duodenal ulcer disease and its various manifestations. Because of the laxity of our present definitions of the various forms of duodenal ulcer disease, some patients get operations for duodenal ulcer even though they do not have that disease. Second, as I have indicated above, we must improve our ability to grade severity and express it in numbers. And finally we must apply decision theory[51] to help us and the patient decide whether the disutility of his symptoms and other manifestations of his dis-

ease are greater than the disutility associated with the risks of operation.

EDWARD PASSARO, JR, MD:* In substituting the concept of severity for intractability, Dr. Grossman is trying to get away from the idea that the patient has somehow failed. I would submit, however, that there are two problems wih this new concept. First, suppose a patient has just had his second episode of symptomatic ulcer disease. His having had a second uncomplicated episode probably would not be considered as indicative of severe ulcer disease. Yet under these circumstances the patient may say: "That's enough; I want my ulcer out." Dr. Grossman, how would your scheme take into consideration the patient's feeling that he has an intractable disease? Second, neither severity nor intractability can be assessed independently of developments in surgery. Suppose, for example, that a new operation is devised that is curative, and has zero mortality and zero morbidity. Then the amount of severity or intractability required for recommending surgical operation would be lessened.

DR. GROSSMAN: Let me answer your second point first. Obviously we are talking about the benefit to risk ratio. Lowering the risks improves the benefit to risk ratio so that the degree of severity (or conversely the amount of benefit to be realized by the surgical eradication of the disease) needed for recommending surgical operation is reduced proportionally.

In regard to your first point you assume that the patient does not get his word in because his physicians are doing the evaluating of the severity of his condition. That assumption is not necessarily correct. In evaluating the benefit to risk ratio, ideally the statements and desires of the patient would always be taken into account in such a formulation. Factors such as time lost from work and time required in hospital because of ulcer symptoms can be weighted in accordance with how important this lost time is to the patient. In so doing, the patient's views are incorporated into severity assessments.

DR. PASSARO: There is a constant attempt to improve the results of surgical treatment for duodenal ulcer disease. Techniques to improve results have included a retrospective analysis of past surgical experience and development of operations designed to reduce some of the sequelae of surgical operation on the stomach.

This discussion focuses on the past experience with operations for duodenal ulcer disease and the circumstances under which one operation is favored over another. Each indication for operative intervention must be considered separately as they vary greatly in their frequency, mode of treatment and results.

One of the problems in making such an assessment is that ulcer disease may not be one disease but a group of diseases so that those operated upon for one complication may have a different clinical history and outcome than the others.

Also, most patients are operated upon for intractability, currently a subjective indication; assessment of the outcome of surgical treatment in them is most often also subjective. Surgical operation carried out for objective complications (such as bleeding, perforation or obstruction), on the other hand, can be judged by the cure or prevention of these complications.

Intractability

Most patients (70 percent) referred to the surgeon for treatment have pain which is considered to be intractable—that is, patient and physician agree that further medical therapy is not warranted. Intractability, however, is a subjective assessment so that in this situation indications for surgical operation are relative, not absolute. This has prompted surgeons to do operations having the lowest incidence of undesirable side effects. Truncal vagotomy and pyloroplasty has been the most frequently employed operation because it can be done expeditiously by most surgeons (reducing the risk of operation) and because it is effective in 60 to 80 percent of patients. Its drawbacks have been twofold: the occurrence of diarrhea or dumping in 1 to 5 percent of patients and recurrent ulcer formation in approximately 10 percent. These two deficiencies have been attributed respectively to the effects of vagotomy on the small bowel and antrum and to an inadequate vagotomy. For these reasons surgeons in Europe have developed a technique to sever vagal branches innervating the parietal cell area of the stomach while sparing vagal branches to the antrum and the remainder of the gastrointestinal tract. Early results from prospective studies conducted abroad indicate this highly selective form of vagotomy (or parietal cell vagotomy) is as effective in curing duodenal ulcer disease as trun-

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cal vagotomy, but the incidence of postoperative diarrhea and dumping have been significantly less. Studies are now being prepared to assess this operation in patients in the United States.

Perforation

While the incidence of perforation is low (1 percent), this complication does not usually escape medical recognition. Because of this, there is better information on the incidence and natural history of this complication of peptic ulcer disease than of others.

Surprisingly, the mortality for ulcer perforation is only about 4 percent. This is due in part to the fact that in perforation the peritonitis is chemical rather than bacterial and the dramatic symptoms this produces cause the patient to seek prompt medical care. In addition, the low mortality is a result of advances in anesthesia and the treatment of shock.

There is considerable debate as to the most effective surgical treatment for a perforated duodenal ulcer. The more conservative group argues that taking care of the immediate problem—peritonitis—is the prime consideration and that definitive treatment can be reserved for later. Therefore, simple closure of the ulcer suffices. An elective operation can be done later with less risk in those patients in whom ulcer symptoms recur (30 to 50 percent).

The other group considers the number of patients in whom definitive treatment is required later to be excessively high. They argue that if at operation the peritoneal soilage is not excessive, and the patient has a previous history of ulcer disease, a definitive operation such as vagotomy and pyloroplasty should be done. In these selected patients there has been no increase in the mortality and morbidity.

Bleeding

Bleeding is the most serious complication of ulcer disease, with a mortality of 10 to 40 percent. Despite the extensive experience with this problem (bleeding is the reason for operating in about a quarter of the patients in whom surgical operation is done), data on the effectiveness of operations and the optimum timing for the operation are lacking and may not be obtainable.

Vagotomy and resection has had the lowest ulcer recurrence rate of any procedure and for this reason has been extensively used to treat bleeding ulcers. Because of the higher operative mortality rate with this operation compared with vagotomy and drainage procedures (especially in emergency situations), vagotomy and drainage in conjunction with ligature of the vessel has been increasingly advocated. It must be realized, however, that the initial lower mortality rate may be offset by an increased incidence of rebleeding among those in whom a vagotomy and drainage procedure has been done (there is recurrence in 2 to 25 percent—average 10 percent—of patients).

Obstruction

Patients with obstruction usually benefit most from surgical treatment of duodenal ulcer disease. Their problem of incomplete gastric emptying can usually be relieved by some mechanical aid to drainage, such as vagotomy and antrectomy or vagotomy and drainage. The latter is generally reserved for elderly, notably debilitated patients in whom a gastric resection would be unduly hazardous. There are no data to substantiate the choice of one operation over the other.

In summary, it is apparent that operation for duodenal ulcer disease continues to evolve. Surgical treatment appears to be safer and increasingly effective with fewer side effects. Barring the development of drugs capable of controlling the ulcer process, surgical operation will continue to be the definitive therapy.

DR. MEYER: Surgical treatment of peptic ulcers must be assessed by asking (1) how effective is the treatment in curing or ameliorating the disease and (2) what undesirable side effects arise from this form of treatment. As with most treatments, information provided in the world's literature bearing on these questions is incomplete, often retrospective, and poorly controlled. The bulk of this literature describes the results of surgical therapy for duodenal ulcer disease which will therefore be the focus of this review.

Effectiveness in Curing Ulcer Disease

How frequently does ulcer disease recur after surgical operation for duodenal ulcer? Recurrence rates vary with the type of operation (Figure 1).

Let us first consider truncal vagotomy with either pyloroplasty or gastroenterostomy, so-called truncal vagotomy with "drainage." Few data are available indicating recurrences over a time span of more than five years. Nobles[52] who followed 104 private patients for more than ten years after

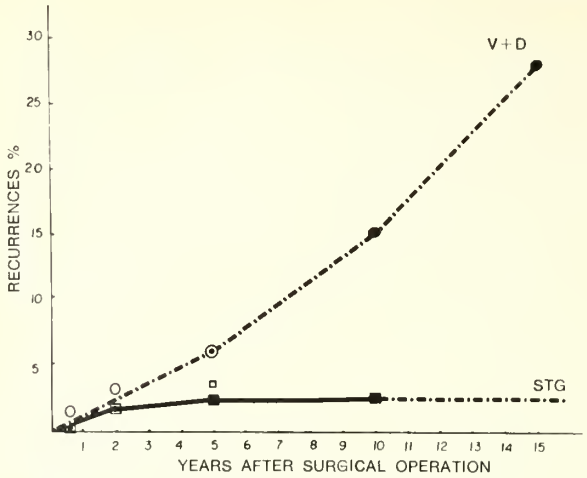

Figure 1.—Percentage of observed recurrences with time after operation. In this figure and in the tables the designation V+D refers to truncal vagotomy and drainage (pyloroplasty or gastroenterostomy), STG indicates subtotal (75 percent) gastrectomy and V+A signifies truncal vagotomy and antrectomy (distal or 50 percent gastrectomy). Closed circles are follow-up data of Nobles after V+D in his private patients; open circles are similar data after V+D among patients in the Veterans Administration's cooperative study.[53] Shaded rectangles are data from follow-up of private patients by McKeown;[55] unshaded rectangles are similar data from the Veterans Administration's cooperative study. Data indicate frequency of ulcer recurrence for the first five postoperative years is identical among private or institutional patients in whom the same operations were done.

operation observed the steady accumulation of recurrences with no fewer than 28 percent of the patients having had an observed recurrence by 15 years after operation. Nobles' observations are corroborated by other studies. In the Veterans Administration's cooperative study[53] the accumulation of observed recurrences in the first five postoperative years conforms almost exactly to the data of Nobles. Stempien's follow-up of patients operated upon at the Long Beach Veterans Administrations Hospital[54] depicted a crude recurrence rate similar to the one shown here, with 25 percent of patients followed for 15 years or more after operation having had an observed recurrence. In none of these studies was the rate of recurrence adjusted for the diminishing number of patients at risk who were followed beyond ten years postoperatively, so that the statistical risk of recurrence is poorly defined but appreciable. Although the recurrence rate after vagotomy is lower than in medically treated ulcer disease, it is disappointing in view of the expected chronic morbidity from this operation (see below).

Recurrence after subtotal gastrectomy is much less common. Again the longest recorded follow-up comes from the private-patient series of McKeown,[55] who followed 800 of his patients for a minimum of ten years after subtotal gastrectomy. We see that the recurrence rate in his study was low (2.6 percent), with all recurrences observed within the first six years after operation (Figure 1). In support of his figures, the Veterans Administration's cooperative study[53] recorded recurrences in 3.7 percent of patients by the end of the fifth postoperative year. After vagotomy plus antrectomy, recurrences are infrequent (0.7 percent) whether at five years in the Veterans Administration's cooperative study[53] or over a considerably longer period of follow-up in Herrington's personal series[56] operated upon at Vanderbilt University. We can conclude from such data that after resective surgical treatment for ulcers —whether done in institutions or private clinics —ulcer recurrence is infrequent and considerably less frequent than after vagotomy with drainage.

The above data bear on ulcer recurrence after elective surgical operation for duodenal ulcer, usually for so-called intractable ulcer disease. Another way of judging the effectiveness of surgical operations for ulcers is to examine how well such operations prevent a complication of ulcer disease which served as the indication for operation. For example, one might ask how well operation for bleeding ulcer disease prevents recurrent hemorrhage. A recent review of this problem[57] indicated that subtotal gastrectomy for hemorrhage associated with ulcer disease frequently—in 5 to 40 percent of cases—failed to prevent recurrent hemorrhage that usually appeared within five years of the index bleed. In most, but not all, of these reports, medically-treated patients rebled nearly twice as often as those treated surgically. Nevertheless, the frequent failure of subtotal gastrectomy to prevent rebleeding is in sharp contrast to low ulcer recurrence rates after subtotal gastrectomy for nonbleeding duodenal ulcers (above). This paradox is further underscored by a lower reported incidence of rebleeding after vagotomy with drainage,[58] an operation clearly inferior to subtotal gastrectomy in the prevention of nonbleeding recurrent ulcer disease (see above). Two reasonable explanations of this paradox might be that (1) ulcer disease in which bleeding occurs somehow differs from ulcer disease in which there is no bleeding, an explanation favored in the literature, or (2) significant numbers of patients with ulcer disease selected for surgical treatment for bleeding were actually bleeding from

other lesions. Either explanation underscores Dr. Grossman's earlier plea for improved nosology in the description of ulcer disease (see above). Because the two other complications of ulcer disease (perforation and obstruction) are much less common, there is scant information detailing how effective surgical operation for these complications is in preventing recurrence of the complication. Definitive surgical treatment for perforation in ulcer disease is apparently effective in preventing not only reperforation but also an otherwise virulent course of chronic ulcer disease after perforation.

In summary, surgical therapy appears more effective in treating virulent ulcer disease than medical therapy. Arguments for the merits or demerits of surgical treatment must hinge on whether the greater effectiveness of this approach is outweighed by postsurgical morbidity or mortality.

Adverse Effects of Surgical Treatment

Operative mortality for elective surgical treatment of ulcer disease is low, about half as frequent as that encountered 15 years ago.[52-56] Emergency surgical operation for hemorrhage carries a variable but considerably higher operative mortality rate. In patients surviving operation there continues to be a long-term mortality rate slightly higher than that in a control population,[59,60] but it is about the same as in medically treated, unoperated patients with ulcer disease. In short, the slight excess mortality from elective surgical therapy is not a serious deterrent for undertaking this form of treatment in virulent ulcer disease.

Rather, it is the likelihood of chronic morbidity from ulcer surgery that remains the principal deterrent to surgical treatment. Both proponents and opponents of surgical treatment acknowledge such surgically-induced morbidity but argue over its prevalence and its severity. Indeed, it is difficult to describe and quantitate the various types of postsurgical difficulties because such descriptions depend upon the subjective response of the patient as well as upon the development of a standard system of recording which would allow comparisons.

In the past 15 years, several institutions[53,61-63] have undertaken prospective trials, using randomly selected patients, of various types of ulcer operations in an effort to create a standard system of evaluation and thereby circumvent the above difficulties. The results of these various studies have been remarkably similar in two respects. First, as already noted, all studies have indicated that vagotomy with drainage is consistently inferior to resective operations with respect to ulcer recurrence, an easily quantitated form of chronic postoperative morbidity. Second, within any one study the incidence of unwanted sequelae such as subjective disability has been similar, regardless of the operation. For example, subjective dysfunction, need for restricted diet to avoid gastrointestinal symptoms, patient dissatisfaction and occupational disability were experienced with equal frequency[53] among significant numbers of patients regardless of the type of operation assigned in the Veterans Administration's cooperative study (Table 10).

Despite these fairly consistent findings within studies, there are unresolved discrepancies among studies which foment continuing debates as to the merits and demerits of surgical therapy for ulcer disease. For example, in contrast to the result of the Veterans Administration study,[53] Kiefer's[64] long-term evaluation of 550 private patients in whom subtotal gastrectomy had been carried out indicated that in only 12 percent were dietary restrictions required and that occupational disability occurred in only 9 percent. It is unresolved whether such striking differences are due to (1) inadequacies in assessment or (2) sociocultural differences between institutional and private patients. Even when results are pooled from many studies in an attempt to average out differences in methods of assessment, striking discrepancies remain. For example, dumping (postcibal abdominal distress with vasomotor symptoms) and diarrhea (more than three bowel movements per day) remain less common in private than institutional patients (Table 11).

We believe these discrepancies in subjective response to surgical operation for ulcer disease among private versus institutional patients arise from socioculturally determined[65,66] variations in perceptions of postsurgical dysfunction. For example, whether or not they were symptomatic, all patients operated upon for ulcers when studied in detail have been found to have profound alterations in alimentary processes as the result of operation.[67,68] Consequently, the better subjective result in private patients is not necessarily evidence that such surgical treatment is free of physiological detriment.

A clinical illustration of this argument (that in many patients, private or institutional, sympto-

TABLE 10.—*Frequency of Subjective Complaints Among Institutional Patients Five Years After Surgical Operation for Ulcer Disease**

	V+D (208 pts) (percent)	*V+A (210 pts) (percent)*	*STG (230 pts) (percent)*
Impaired strength (patient's statement)	43.5	42.5	45.3
Restricted diet	37.8	39.8	43.6
Work lost	18.1	22.6	17.6
Poor to fair result (Patient's statement)	15.1	13.4	9.4

V+D signifies vagotomy and drainage
V+A is vagotomy and antrectomy
STG indicates subtotal gastrectomy

*From the Veterans Administration's cooperative study.[53]

TABLE 11.—*Frequency of Gastrointestinal Complaints Among Patients Two or More Years After Surgical Operation**

	V+D (percent)	*V+A (percent)*	*STG (percent)*
Dumping	23.2 VA	29.4 VA	38.8 VA
	18.2 Univ	24.6 Univ	22.4 Univ
	12.4 Private	....	6.8 Private
Diarrhea	18.5 VA	21.6 VA	16.5 VA
	21.4 Univ	23.2 Univ	6.5 Univ
	16.2 Private	....	....

V+D signifies vagotomy and drainage
V+A is vagotomy and antrectomy
STG indicates subtotal gastrectomy

*Comparisons are made between institutional and private patients with published data from two Veteran Hospital studies (VA),[50,59] one university (Univ) study[61] and three follow-up studies of patients from private practice.[52,55,64]

matic or asymptomatic, there are significant physiological derangements as a result of operation for ulcer disease) is provided by data on the development of postoperative anemia. After such operation, many patients lose weight, and specific nutritional deficiencies develop in some which give rise to metabolic bone disease[69] or peripheral neuropathy.[70,71] Unfortunately, the literature does not describe postoperative weight loss in a standard fashion which allows statistical compilation; and the prevalence of metabolic bone disease or peripheral neuropathy varies with the application and sensitivity of methods used to assess those abnormalities. However, most clinical reports routinely describe blood hemoglobin concentrations so that extensive comparisons can be made among reports of the outcome of such surgical treatment. Following operation for ulcer disease there is a progressive decline with time in the mean blood hemoglobin concentration.

The increasing prevalence of anemia is associated with a parallel decline in serum iron, and, in some cases, in serum B_{12}, both of which are inefficiently absorbed following surgical operation for ulcers. There is no correlation between the development of anemia and the subjective symptomatic result[55,72,73] but by ten years or more after subtotal gastrectomy no fewer than 30 percent of patients[55,69,72] have anemia. Long-term evaluations of patients in whom truncal vagotomy with drainage has been done—that is, nonresective surgical operation—indicate similar prevalence of anemia and iron deficiency 15 to 20 years after operation.[74-76]

In summary, current surgical treatment is effective in curing ulcers at only slight risk of operative mortality for an elective operation. The significant prevalence of subjective, chronic morbidity and objective nutritional impairment following these operations is the major deterrent against a wider application of this form of treatment. Nevertheless, surgical therapy continues to evolve as surgeons search for new operations that combine effectiveness with a lower incidence of chronic side effects.

DR. GROSSMAN: How likely is it that a new operation, proximal gastric vagotomy, will change the outlook for patients in whom surgical therapy is required?

DR. MEYER: There are two aspects to that question: (1) how effective is this new operation in curing ulcer disease and (2) does it produce less chronic morbidity. In regard to the first aspect, there are conflicting reports after five years of trials in Europe, one group claiming ulcer recurrence in as few as 5 percent of patients and another group, in as many as 20 percent. It is my guess that the more time that elapses after proximal gastric vagotomy, the higher will be the ulcer recurrence rate—just as after truncal vagotomy. Nevertheless, we need data, not guesses. In terms of chronic postoperative morbidity (the risk side of the benefit to risk ratio), it is already apparent that this new operation is much less frequently associated with postoperative symptoms (dumping or diarrhea) or objectively measured derangements in alimentary functions. What we need are more studies to determine whether the ulcer cure rate (benefit) is high enough to recommend this operation in place of the others.

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Refer to: Sarcoidosis—Medical Staff Conference, University of California, San Francisco. West J Med 126:288-296, Apr 1977

Sarcoidosis

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Associate Professor of Medicine, and H. David Watts, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, CA 94143.

DR. SMITH:* *It has been our custom to ask our chief medical residents at Moffitt Hospital to discuss a topic at Medical Grand Rounds near the conclusion of their residency year. We have been privileged to have Dr. James K. Brown as chief resident during this past year. Consistent with his special interest in chest medicine, he has elected to present the case of a patient with sarcoidosis and to discuss selected aspects of that remarkably varied illness.*

DR. BROWN:† The patient is a 26-year-old black woman with a history of a seizure disorder and a finding of bilateral hilar adenopathy on x-ray studies of the chest. Because a new parenchymal pulmonary infiltrate was noted, the patient was admitted to the University of California Medical Center in December 1975.

In 1968 psychomotor seizures had developed, and an electroencephalogram showed a right temporal focus. Findings on brain scan, lumbar puncture and x-ray study of the chest were within normal limits, and a therapy with diphenylhydantoin (Dilantin®) was begun. In 1972 the patient was admitted to the medical service for evaluation of weight loss and continued seizures. On physical examination submandibular, cervical and axillary adenopathy was noted, but findings were otherwise normal. Routine admission laboratory studies gave results within normal limits. Bilateral hilar and right paratracheal adenopathy with otherwise clear lung fields were seen on an x-ray study of the chest. An axillary lymph node biopsy showed hyperplasia consistent with the diagnosis of pseudolymphoma caused by diphenylhydantoin. The anticonvulsant regimen was changed to phenobarbital and primidone (Mysoline®) and the patient was discharged. On a follow-up x-ray film of the chest in 1973, resolution of the mediastinal adenopathy was seen, but the patient continued to lose weight and to have occasional seizures.

In December 1975 a follow-up film of the chest showed parenchymal infiltrates, and although there was no complaint of respiratory symptoms, the patient was admitted for evalua-

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tion. On examination the patient was noted to be thin and vital signs were within normal limits. Examination of the skin and eyes showed no abnormalities. Shotty cervical, epitrochlear and inguinal adenopathy was noted. Chest, cardiac and abdominal examinations were unremarkable. There were no localizing neurological findings. Hematocrit reading was 38 percent, leukocyte count 5,400 per cu mm.[3] The serum calcium and liver function tests gave results within normal limits. On an x-ray study of the chest diffuse, fine reticulonodular infiltrates and right paratracheal fullness were seen. Pulmonary function tests showed a slight decrease in the vital capacity and total lung capacity, an increase in the forced expiratory volume in one second—forced vital capacity ratio (FEV_1/FVC) and a normal diffusing capacity. A finding on a transbronchial biopsy was noncaseating granulomata consistent with sarcoidosis, and the patient was discharged on a regimen of anticonvulsants only. On follow-up x-ray film of the chest four months later partial clearing of the pulmonary infiltrates was seen.

This patient's illness illustrates several features quite typical of sarcoidosis. First, the onset of the illness was in the patient's early 20's. In Sharma's recent large series from Los Angeles,[1] about two thirds of all patients with sarcoidosis presented in the third or four decades.

Secondly, if we ignore the seizure disorder in this patient or ascribe it to other causes, the illness presented as weight loss—a presentation quite compatible with sarcoidosis. Again, in Sharma's series, about a fourth of the patients presented with constitutional symptoms (weight loss, fever, anorexia), and half with respiratory symptoms (dyspnea, cough, chest pain). Twenty percent of cases were picked up incidentally because of abnormalities seen on films of the chest, and a small fraction presented with symptoms referable to localized extrathoracic disease.

Third, the illness occurred in a black person, and sarcoidosis in the United States affects blacks about ten times as frequently as whites.

Fourth, the progression of pulmonary involvement in this case, that is the appearance of bilateral hilar adenopathy followed by parenchymal interstitial infiltrates, is the rule in sarcoidosis. A reverse progression, that is from parenchymal disease to hilar or mediastinal involvement, has not been described in a single case of sarcoidosis and should suggest other diagnoses, such as lymphoma or Hodgkin disease.

Finally, the course of illness in this patient, particularly its indolent progression and its tendency to spontaneous remission, is quite compatible with sarcoidosis. On the other hand, there is one aspect of this case that is atypical for sarcoidosis; the original lymph node biopsy failed to show noncaseating granulomata. Israel and Sones have pointed out that peripheral, easily accessible tissue, such as lymph nodes and skin lesions, have a high histologic yield in sarcoidosis.[2] In their series, the biopsy of a palpable lymph node showed typical granulomata 80 to 100 percent of the time, depending on the site from which the node was taken. Typical sarcoid skin lesions always showed granulomata. A potential problem of the granulomata found in these peripheral sites is their lack of specificity, and I will be commenting more about this later. The fact that a biospy study of the axillary node in this patient failed to show granulomata in 1972 raises the possibility that diphenylhydantoin-induced lymphadenopathy was present. However, arguing against the diagnosis is the frequency of diphenylhydantoin-related cases of associated hypersensitivity phenomena, such as fever, rash and eosinophilia—none of which were present in this patient. Also, hilar adenopathy is an extraordinarily unusual manifestation of the diphenylhydantoin pseudolymphoma syndrome; and, in fact, the association has been reported in only a single case.

Today I would like to discuss three aspects of sarcoidosis which at present seem the most important and controversial: first, pulmonary sarcoidosis, with reference to the patient presented; second, the use of corticosteroids in sarcoidosis, both for its thoracic and extrathoracic manfestations; third, a few words about the continuing search for the cause of sarcoidosis.

Pulmonary sarcoidosis can be divided into certain radiologic stages. In about 10 percent of cases the initial x-ray film of the chest shows no abnormalities (stage 0). Siltzbach believes that such patients may actually have a relatively late stage of the disease, the original lung involvement having been asymptomatic and having undergone spontaneous remission. About 50 percent of the chest films show bilateral hilar adenopathy when the patient is first seen (stage 1), 25 percent show bilateral hilar adenopathy associated with peripheral infiltrates (stage 2) and 15 percent show parenchymal infiltrates only (stage 3).

There are a number of interesting features of

the bilateral hilar adenopathy syndrome: (1) It is associated with right paratracheal adenopathy in about 50 percent of cases. The reason for the asymmetry of the nodal involvement at the paratracheal level in contrast to the bilaterality at the hilar level is not known, but unilateral right paratracheal adenopathy also occurs in other diseases affecting the mediastinum, such as primary tuberculosis and lymphoma. (2) In sarcoidosis the granulomatous process in the hilar nodes tends to be nonaggressive and noninvasive. By this I mean that erosion into the bronchi is rare, as is compression and narrowing of the bronchial lumina. Also, the pathological process is only very rarely protracted and destructive enough to leave the nodes calcified. All three of these features which are very rare in sarcoidosis—erosion, compression and calcification—do occur in other conditions affecting the mediastinum, such as primary tuberculosis. (3) While rarely associated with pulmonary symptoms, the bilateral hilar adenopathy syndrome is associated with certain extrathoracic symptoms, particularly erythema nodosum and anterior uveitis. (4) Even in the absense of radiologic infiltrates at this stage of the disease, the parenchyma of the lung does show pathologic changes, thickened alveolar membranes and granulomata scattered through the interstitium. It is perhaps not surprising, therefore, that Sharma was able to show there to be pulmonary function abnormalities at this stage, the most consistent findings being reduction of the diffusing capacity and static lung volumes. The prognosis in this group is excellent with complete remission in about 75 percent of cases.

To what extent a thorough diagnostic evaluation is necessary in patients presenting with bilateral hilar adenopathy is a controversial issue. As a general rule, the diagnosis of sarcoidosis at any stage is a three-step progress. First, one must have compatible clinical features; second, noncaseating granulomata must be found in one or more organs; third, other specific causes of granulomatous disease must be ruled out by appropriate special stains, skin tests and serologies.

In the case of the bilateral hilar adenopathy syndrome, some have stated that the latter two steps are unnecessary. For example, in a retrospective fashion Winterbauer studied the cases of 88 patients presenting with bilateral hilar adenopathy in Seattle, Washington.[3] Of the 74 patients who subsequently were found to have sarcoidosis, 29 had been asymptomatic, with no abnormalties on physical examinations, and 13 had had erythema nodosum or uveitis when first seen. Of 20 patients found to have lymphoma, bilateral hilar adenopathy, when it occurred, tended to be a late manifestation of the disease, having been seen on x-ray studies in only eight at presentation; all eight were symptomatic generally with nonspecific systemic symptoms, and in seven of eight easily palpable extrathoracic tumor was noted at presentation. Four patients with bronchogenic carcinoma and two patients with metastatic extrathoracic tumors were found who presented with bilateral hilar adenopathy, and all had had symptoms and easily palpable tumor.

These results led Winterbauer to the following conclusion: a patient presenting with bilateral hilar adenopathy, without symptoms or physical abnormalities or with erythema nodosum or anterior uveitis, has sarcoidosis, and in such a patient no further study is necessary. In addition, Winterbauer was able to identify certain factors which, even when associated with bilateral hilar adenopathy, were so atypical for sarcoidosis that further evaluation was always indicated. These findings were pleural effusions, anterior mediastinal adenopathy and severe anemia. One problem with this approach is that it is sometimes unsatisfying to base a diagnosis on the absence of symptoms or findings, particularly when the other conditions in the differential diagnosis are of such a serious nature. Some still feel that in patients with bilateral hilar adenopathy a tissue diagnosis is required.

What tissue might one biopsy in such cases? A relatively new procedure used to obtain parenchymal lung tissue is the transbronchial biopsy. It has a number of advantages: first, it has a relatively high diagnostic yield, probably in the 60 to 80 percent range; second, the procedure permits visualization of the tracheobronchial tree, which may be useful in ruling out conditions other than sarcoid, such as bronchogenic carcinoma or tuberculosis, and finally, the procedure is associated with a low complication rate, pneumothoraces developing in a low percentage of patients. Therefore, at present a transbronchial biopsy is probably the procedure of choice for obtaining a tissue diagnosis in suspected pulmonary sarcoid.

The x-ray films in Figures 1 through 6 show examples of the parenchymal lung disease of sarcoidosis. Figure 1 shows bilateral hilar adenopathy with a rather fine reticulonodular infiltrate

—and in this patient there also has been a spontaneous left pneumothorax, a well recognized complication of pulmonary sarcoid. Figure 2 shows more advanced disease, probably with early pulmonary fibrosis. A close-up of the right lung (Figure 3) shows a coarse linear and nodular infiltrate with honeycombing. Figure 4 is an example of end-stage pulmonary fibrosis secondary to sarcoid with characteristic irregular strands extending out from the hilum and bullous formation at the apices and base. It is primarily at this stage of the disease and within the apical bullae that aspergillomas may form. The last two x-ray films show atypical forms of pulmonary parenchymal disease: first, alveolar or acinar sarcoid

Figure 1.—Bilateral hilar adenopathy, reticulonodular infiltrate, left pneumothorax. (X-ray studies courtesy of Dr. Gordan Gamsu, University of California, San Francisco, Department of Radiology.)

Figure 2.—Advanced interstitial lung disease related to sarcoidosis.

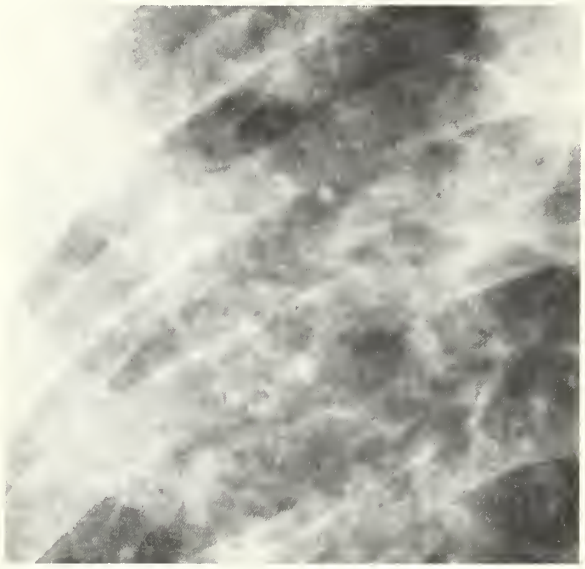

Figure 3.—Close-up of right lower lung field from Figure 2, showing coarse reticulonodular infiltrate and early honeycombing.

Figure 4.—End-stage pulmonary fibrosis secondary to sarcoidosis with bullous disease and cor pulmonale.

(Figure 5) and second, nodular sarcoidosis (Figure 6). Interestingly, the latter two patients were asymptomatic at the time the x-ray studies were done.

I should like to turn now to the problem of the treatment of pulmonary sarcoid. Roughly a third of all patients with sarcoidosis receive glucocorticosteroids at some point in their illness, and the major indication is pulmonary disease. Yet, definitive data with respect to the efficacy of steroids in pulmonary sarcoid have not been gathered, for reasons which I think will be evident. What is the prognosis of pulmonary sarcoid in the untreated state? During the 1940's and 1950's Smellie and Hoyle followed a large series of patients with untreated pulmonary sarcoidosis for periods of between 2 and 20 years.[4] Of those with bilateral hilar adenopathy alone at entrance into the group (roughly 40 percent of the total group), in three quarters there was complete remission and in one quarter the later development of parenchymal disease was shown radiographically. Of those with parenchymal infiltrates, either at entrance to the study or subsequent to hilar adenopathy, the infiltrates cleared in half the patients and persisted for more than two years in the other half. Of those with persistent infiltrates, in roughly a third there was progression shown on x-ray studies to full-blown fibrosis. The percentage of the total group with radiographic fibrosis at the end of the study was 13 percent. Clinically, at the end of the study, 87 percent of the patients were well, 3 percent were disabled by pulmonary disease and 10 percent had died, primarily of respiratory failure.

Figure 5.—Alveolar of acinar sarcoidosis.

Figure 6.—Nodular sarcoidosis.

The disease, then, has a reasonably benign outcome, even in the untreated state. What is the evidence for the use of steroids? Most of it comes from a series of retrospective and somewhat anecdotal studies. The experience of most authors has been that dyspneic patients will improve symptomatically on a regimen of corticosteroids, except perhaps those with end-stage fibrotic disease. Also, steroids nearly always shrink pulmonary infiltrates, again except in the fibrotic group. The effect on pulmonary function is more variable. Generally the lung volumes improve, while the diffusing capacity remains low. This discrepancy may be a reflection of the fact that steroids promote healing of granulomata by fibrosis. As the granulomata shrink, there is more room for inspired air to come into the alveoli and the total lung capacity increases. But at the same time there is persistence or even extension of the fibrotic process along the alveolar walls causing continued abnormalities of diffusion. Most authors also acknowledge that on rare occasions pulmonary sarcoidosis may enter a fulminant, rapidly progressive phase; and in these instances the course may be dramatically reversed with administration of steroids.

There have been two recent prospective studies evaluating the effects of steroids. The first, by Young and co-workers,[5] included 25 patients

with pulmonary sarcoidosis in whom resting oxygen partial pressure (Po_2) was less than 80 mm of mercury and in whom diffusing capacity was abnormal. Alternate patients received prednisone or placebo. Over a long follow-up period the authors were unable to observe any differences between the two groups. Unfortunately, this study included a relatively small number of patients, and the patients tended to be relatively well from the start. Israel and Fouts[6] studied 90 patients with pulmonary sarcoidosis. Again, alternate patients received prednisone or placebo. At a three-month follow-up, in treated patients with parenchymal disease at the start of the study, there was improved clinical, radiographic and spirometric status compared with the controls, but over the long-term there were no detectable differences between the two groups.

Assuming that certain patients with pulmonary sarcoidosis benefit at least transiently from steroids, how should steroids be given and what problems may they cause? Dr. Carol Johns in Baltimore has recently published her experience with the use of glucocorticoids in 150 patients with symptomatic pulmonary sarcoid.[7] The treatment schedule she recommends is shown in Table 1. Of note is the fact that despite the careful approach to withdrawal of corticosteroids, over 75 percent of Dr. Johns' patients relapsed during the reduction period, usually when the steroid dose had reached 15 mg or below. As a result, in about half of her patients, once administration of prednisone was started it was required for over two years.

What conclusions can be drawn with respect to the use of corticosteroids in pulmonary sarcoidosis? As yet, there is no evidence that the early use of corticosteroids prevents the occasional development of pulmonary fibrosis. It is easy to see why a large prospective study testing this point has never been carried out. Since there will be a progression to fibrosis in only a small fraction of patients with untreated pulmonary sarcoid, assessing the long-range protective effect of steroids would require giving large numbers of patients high doses of steroids for prolonged periods. Steroids, then, are probably only indicated for symptomatic relief of dyspnea in pulmonary sarcoidosis. Once started they may have to be given for prolonged periods because of the problem of relapse.

There are a variety of extrathoracic manifestations of sarcoidosis which on occasion require steroid therapy. Hypercalcemia is a particularly interesting manifestation of the disease since it is one of the few not directly attributable to granulomatous infiltration of a specific organ or tissue. In most patients with sarcoidosis there is hyperabsorption of calcium from the gastrointestinal tract, and this observation, along with a variety of others, has suggested a fundamental hypersensitivity to vitamin D in sarcoidosis. In the untreated state in most patients with sarcoid there are undetectable parathormone levels in the serum, presumably due to transient, imperceptible rises in the serum calcium level. Depending on the series, hypercalciuria occurs in between 10 and 30 percent of patients with sarcoid, but in only a very small fraction do renal stones develop. The incidence of sustained hypercalcemia is probably quite low, in the range of 2 to 3 percent. The treatment of choice is a short course of corticosteroids, although occasionally dietary restriction of calcium and vitamin D will suffice.

TABLE 1.—*Prednisone Treatment Schedule (after Johns[7])*

40 mg, 30 mg (divided daily doses)	2 weeks each
25 mg (single AM dose)	2 weeks
20-15 mg (single AM dose)	5 months
12.5, 10, 7.5, 5.0, 2.5 (single AM dose, with careful observation during tapering and retreatment if relapse occurs)	2 weeks each

Sarcoid affects the nervous system in about 5 percent of cases. Cranial and peripheral neuropathies tend to occur early in the disease and are usually transient. Seventh nerve palsy is the most frequent manifestation of neurosarcoid. Rarely basilar meningitis develops; and when it occurs, the granulomatous process may invade structures at the base of the brain, producing diabetes insipidus in a high percent of cases, hydrocephalus, optic atrophy, ataxia and a variety of hypothalamic disturbances. The basilar meningitis, in contrast to the neuropathies, usually occurs in a patient with previously well known chronic sarcoidosis. It often, but not always, responds to steroid therapy. At autopsy granulomata are found in the myocardium in about 20 percent of cases with sarcoidosis, but clinical cardiac symptoms or significant electrocardiographic findings occur in only about 5 percent. Conduction abnormalities are the most common findings, but disorders of impulse formation, particularly ventricular arrhythmias, may occur. Rarely, congestive failure related to infiltration of the myocardium de-

velops, and in the latter instance most would recommend a trial of steroids, although the results are often not beneficial. Clinically significant ocular sarcoid appears in about 15 percent of cases. The most common manifestation is acute anterior uveitis which presents as the sudden onset of redness and watering of the eyes, often associated with bilateral hilar adenopathy and erythema nodosum. A more serious complication is chronic iridocyclitis, which usually presents as the insidious onset of pain and blurring of vision. Unless there is vigorous treatment with topically or systemically given steroids, secondary glaucoma, cataracts and blindness develop in many of these patients.

I should like to turn now to some more recent developments in the continuing search for the cause of sarcoidosis. The major contributions have come from three groups: epidemiologists, immunologists and microbiologists.

Epidemiologists have expended tremendous amounts of shoe leather and computer time in an effort to pin a specific cause on sarcoid, and they have turned up several interesting findings. First, judging from a study of autopsies done in Malmo, Sweden, most cases of sarcoid are subclinical. The investigators in that study found that the autopsy incidence of disseminated noncaseating granulomata was 6 per 1,000. The clinical incidence of sarcoid in that region of Sweden is about 0.6 per 1,000, or a tenth of that reported in the autopsy series. Since the diagnosis of sarcoidosis rests on both clinical and pathological grounds, it is difficult to interpret the Malmo autopsy findings, but they do suggest that many cases of sarcoidosis go undiagnosed.

Second, in the United States the disease is about ten times more common in blacks than in whites. Interestingly, early studies suggested that sarcoidosis was quite uncommon in blacks in Africa. However, a recent careful study by Morrison from Pretoria found that sarcoidosis there is about ten times as common in Bantus as in the local white population, a ratio of racial prevalence equal to that in the United States.[8] Also interesting is that many of the sarcoid-affected tribesmen originally had been misdiagnosed and put into leper colonies, a situation reminiscent of that in the United States in the past when sarcoid patients were often mistakenly put into tuberculosis sanitaria. In contrast to the high incidence in blacks, sarcoidosis rarely develops in American Chinese, American Eskimos and American Indians (such cases are reportable). This finding is of interest because in these three ethnic groups there is a very high incidence of tuberculosis.

Third, Siltzbach feels that sarcoidosis is a disease of immigrants. He points out that the disease is more common in the Irish and West Indian populations in London than in native Londoners, in the Martinique population in Paris than in native Parisians, in Puerto Ricans in New York City than in native New Yorkers and in the Mexican population in Los Angeles than in the natives there. The problem with these data is that they are one-sided; careful prevalence studies have not been done in Ireland, the West Indies, Martinique, Puerto Rico and Mexico. Until they are, it is difficult to conclude that the act of immigration per se has anything to do with the occurrence of sarcoidosis in the immigrants.

Finally, in the early 1950's a large Veterans Administration study in the United States purported to show that sarcoidosis was more common in the Southeastern United States than in other parts of the country. This finding gave birth to a number of interesting and colorful theories about the cause of sarcoid. One was the pine-pollen hypersensitivity theory, which has since been disproved. Another was the pica theory. A group of medical geologists apparently found that the beryllium content of the soil in the Southeastern United States is higher than elsewhere, and they attempted unsuccessfully to show that sarcoid occurred more frequently in clay-eaters. More recent epidemiologic studies have shown that when the racial distribution of the population is accounted for, sarcoidosis occurs at about equal frequency in all parts of the country. What the epidemiologic studies have shown, therefore, is that sarcoid has certain, definite racial predilections.

Immunologists have made some recent interesting observations relating to the depression of cellular immunity often observed during the course of the illness. There are several relevant aspects of this phenomenon. The first is that it appears to be an acquired and not an inherited defect in patients with sarcoid. This fact was established during the course of a large British bacille Calmette Guérin (BCG) study carried out in the 1950's. Findings on purified protein derivative (PPD) skin tests and on x-ray studies of the chest were followed in large numbers of patients, both vaccinated and unvaccinated with BCG. It was found that in those in whom sarcoidosis happened

to develop during the course of the study, there was no correlation between the occurrence of the disease and previous PPD skin test status.

A second feature of the depression of cellular immunity is that it appears to be a relative and not an absolute anergy. For example, it has been shown that patients with sarcoidosis usually retain the ability to reject homologous skin grafts, a capacity that patients with Hodgkin disease, for example, usually lose. Of more clinical relevance, it has been shown that when tuberculosis develops in an anergic patient with sarcoid, the PPD skin test converts to positive. It is as if the cellular immune system in sarcoid retains the ability to respond to particularly strong stimuli.

Third, it appears that in patients with sarcoidosis there is either no increase, or perhaps only a mild increase, in susceptibility to infection. There is no increased incidence of viral infection, similar to the occurrence of herpes zoster in Hodgkin disease, for example. The incidence of tuberculosis in patients with sarcoid is diminishing and now appears to be only about 2 percent. There is no increased incidence of fungal disease in patients with sarcoid, except for the occurrence of aspergillomas, and these appear to be more related to structural changes in the lung than to a systemic decrease in cellular immunity.

What is the mechanism of this mild depression in cellular immunity? First, in about a third of patients with sarcoidosis there is mild lymphopenia; and when the lymphocyte subpopulations are carefully studied, as they have been recently by Hedfors and co-workers,[9] the deficiency appears to be predominately in the T-cell series.

Second, the ability of T-cell mitogens, such as phytohemagglutinin, to stimulate lymphocyte transformation is reduced in patients with sarcoidosis. Recently Mangi and co-workers tested transformation of normal lymphocytes in the presence of sera from patients with sarcoidosis and presented evidence for a serum inhibitor of lymphocyte transformation in patients with sarcoid.[10] The source of the serum factor is not known. Mangi has postulated that it may be produced by the stimulated lymphocytes themselves, so that it may represent a kind of feedback inhibitor for the cellular immune system.

Finally, how about the search for a specific microbiologic cause of sarcoidosis? In this regard there have been two recent studies of interest, one clinical and one from the laboratory. The first is a study by Kent carried out on 30 patients originally diagnosed as having sarcoid on the basis of compatible clinical features and a peripheral tissue biopsy (scalene fat pad, skin or lymph node) showing noncaseating granulomata.[11] In each patient a series of cultures, skin tests and serologic tests was done in the search for a specific infectious cause. If none was found, open lung biopsy was done and specimens of tissue were taken from the pleura, lung and mediastinum for study. Surprisingly, in 27 of 30 cases, a specific diagnosis other than sarcoid was made, the most common being tuberculosis. It is difficult to know what to say about this study. On the one hand the differences between classic tuberculosis and sarcoidosis are so overwhelming that in most instances the two must represent separate diseases. On the other hand, the results of Kent's study stand unchallenged because no one since has carried out such a vigorous diagnostic approach in a group of patients with ostensible sarcoid. A second group of studies of great interest have been the ones by Mitchell in which he has injected sarcoid splenic homogenates into the footpads of mice.[12] Six months later biopsies of the footpads showed classical noncaseating granulomata in most cases. Preirradiation of the homogenates prevents granulomata formation.

In a second, more recently published study, Mitchell has been able to carry out passages from the original footpads to a second generation of mice. This appears to be good evidence for the existence of a transmissible etiologic agent in sarcoid.

From a historical point of view, where are we in our understanding of this disease? Emanating from Northern Europe in the late 19th Century, the original reports of sarcoid were clinical and descriptive. Because sarcoid is a disease with protean manifestations, a variety of colorful eponyms were generated: Mortimer malady, after Jonathan Hutchinson's original patient, Mrs. Mortimer, who had typical skin manifestations of sarcoid; Boeck sarcoid, after Cesar Boeck, a famous Norwegian dematologist; Heerfordt syndrome, after the Danish ophthalmologist who described the association of fever, uveitis, parotitis and cranial nerve palsies. It was not until many years later that Jorgen Schaumann, a Swedish pathologist, tied the syndromes into a single disease by showing the epithelioid granulomata to be their common pathologic hallmark.

It is interesting to read Hutchinson's account of his encounter with Mrs. Mortimer.[13] "She had,"

he said, "multiple raised, dusky red patches over her body." Hutchinson actually had wanted to do a biopsy of one of these lesions, but ran into a problem common even in this day and age. "I suggested to her," he writes, "that a portion of her skin be removed for microscopic examination with the result that I did not see her again."

TRADE AND GENERIC NAMES OF DRUGS

Dilantin® ..... *diphenylhydantoin*
Mysoline® ..... *primidone*

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Analgesic Drugs as Alternatives to Ergotamine in the Treatment of Vascular Headache

About half of the patients who use ergotamine would prefer their headache to the side effects of the ergotamine. And in these, probably a better approach, if the headaches are infrequent, is to provide them with reasonably adequate analgesia. The amount of analgesia required for a severe attack of migraine is really very considerable: at least half a grain of codeine or 100 mg of meperidine (Demerol®), occasionally helped by a small dose of some agent to reduce nausea, for which I prefer either 5 or 10 mg of chlorpromazine (Thorazine®), rather than prochlorperazine (Compazine®). Compazine creates enormous business for the neurologist and brings people to our emergency rooms with their teeth stuck together or their heads stuck back on their necks somewhere with one of these prochlorperazine dystonias, which I find quite unnecessary to produce. . . . I don't see what it does that chlorpromazine won't do.

I do think that the abuse of ergotamine continues to be a problem. I just never know—when I see a person who's used intermittent ergot and who then has a myocardial infarct or a stroke or develops some other vascular complication—what the role of the ergot is. But I think, sometimes, it's more significant than my neurological colleagues are willing to admit. I am personally very reluctant to prescribe ergotamine, except as a measure of desperation in the adult. I will use it in teenagers for infrequent vascular headache, with very strong precautions about its use, limiting them to not more than 6 mg in a day, and not more than 10 mg in any week, and with periods of enforced abstinence.

—STANLEY VAN DEN NOORT, MD, *Irvine, CA*

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Important Advances in Clinical Medicine

Epitomes of Progress—Obstetrics and Gynecology

The Scientific Board of the California Medical Association presents the following inventory of items of progress in obstetrics and gynecology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly estabished, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in obstetrics and gynecology which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Obstetrics and Gynecology of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, California Medical Association, 731 Market St., San Francisco, CA 94103

Efficacy and Safety of Prenatal Genetic Amniocentesis

BETWEEN July 1, 1971, and June 30, 1973, nine American prenatal diagnosis centers collected and pooled information on amniocentesis. Data on 1,040 patients and 992 controls were analyzed.

In 91.3 percent of the patients amniocentesis was done for cytogenetic indications and in 8.7 percent for metabolic reasons. Abnormal fetuses were diagnosed in 2 percent of women over the age of 35, in 1.5 percent of women who previously had had a child with Down syndrome and in 16.7 percent of balanced translocation carriers. In patients at risk for X-linked or autosomal recessive conditions, fetal abnormalities were diagnosed in numbers consistent with the calculated probabilities. Six erroneous diagnoses were made (three of them involving only the sex of the infant), so that the accuracy of the procedure was 99.4 percent.

There were no differences as to maternal or fetal complications between the patients and the controls. Rates of fetal loss (spontaneous abortions, *in utero* deaths and stillbirths) were similar. Both at newborn examination and at reevaluation one year later, the offspring in the two groups appeared comparable.

Interestingly, the use of ultrasonic placental localization did not appear to reduce maternal complications or fetal loss. A finding worthy of note was the fact that the incidences of both vaginal bleeding and fetal loss increased with increasing numbers of needle insertions; the differences were statistically significant for bleeding. This suggests that taps should not be done unduly early in pregnancy (16 menstrual weeks seems optimal in our hands) and should not be done by personnel who are not well experienced in the procedure.

In summary, the rate of serious side effects secondary to amniocentesis probably does not

exceed 0.5 percent. Hence amniocentesis should be considered by all pregnant women over the age of 35, women who have previously borne a baby with a chromosomal anomaly, persons with a history of Down syndrome in close relatives, balanced translocation carriers, known or suspected carriers of X-linked or autosomal recessive conditions, and women who have given birth to children with neural tube defects (where the recurrence risk is 5 percent, and diagnosis can be made by analysis of the amniotic fluid for alpha-fetoprotein). Amniocentesis has now been shown to be both safe and accurate.

LAURENCE E. KARP, MD

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Ultrasound and Gynecology

AT ONE TIME or another, even the most experienced examiner has questioned his evaluation of a patient's pelvic viscera. New physicians are taught that good medicine dictates an examination under anesthesia before pelvic laparotomy. Ultrasound offers clinicians an additional noninvasive diagnostic technique. Ultrasound may assist in the following situations:

- Extrauterine pregnancy
- Tubo-ovarian abscess
- Cystic ovarian masses
  Cystadenomas
  Cystic teratomas
- Solid ovarian masses
- Complications of dilation and curretage (creation of false passage within the myometrium, periuterine hematomas, and so forth)
- Uterine foreign bodies (including intrauterine devices)
- Documentation of suspected or unsuspected pregnancy in the presence of other uterine pathology
- Demonstration of gestational sac for amniotomy

In each of the listed situations the findings may not be clear enough to indicate a specific diagnosis; however, the ultrasonographer should be able to confirm or disprove the clinician's suspicions concerning the presence and size of a lesion. Moreover, in a significant number of cases the echographic findings will be specific enough to indicate more appropriate management than that contemplated before the test was done.

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A Modern Approach to the Management of Intrauterine Fetal Death

KNOWLEDGE of a retained dead fetus is a source of considerable mental distress, inconvenience and anxiety to a patient. The prospect of carrying a dead fetus *in utero* even for a few days tends to be emotionally traumatic. While 90 percent of such patients will go into spontaneous labor within four weeks, even this period of time can be psychologically distressing. Usually if the patient delivers before four weeks there are no medical sequellae or complications. However, a retained dead fetus beyond four weeks occasionally poses a serious hazard to the pregnant woman. Coagulation defects have been observed in 40 percent of patients with retention of the dead fetus beyond six weeks. Therefore, the woman who has a retained dead fetus beyond four weeks must be followed closely with weekly and possibly biweekly fibrinogen levels to determine whether this specific serious complication is occurring. Obviously it would be safer and more convenient to evacuate the uterus as soon as confirmation of death *in utero* is established.

All too frequently the cervix is not favorable or responsive to oxytocin stimulation. For this reason many physicians in the past have employed the approach of watchful expectancy in the hope that spontaneous labor may ensue with resultant delivery in an appropriate period of time.

Many studies in the literature attest to the successful use of prostaglandins to terminate pregnancy at any stage of gestation. Trials of prostaglandins $F_2\alpha$ and E_2 for induction of labor at or near term have shown them to be as effective as oxytocics in initiating labor and producing a normal labor pattern and successful outcome. Recently, prostaglandins E_2 vaginal suppositories have been introduced as part of the armamentarium of the obstetrician.

In 1976 Southern and Gutknecht reported on 212 patients diagnosed as having missed abortion or intrauterine fetal death. These patients were managed by the use of prostaglandin E_2 vaginal suppositories. These suppositories, containing 20 mg of prostaglandin E_2 in a lipid base, were inserted into the posterior fornix at three- to five-hour intervals. In 98 percent of these patients there was successful evacuation of the uterine contents without serious side effects. All patients were either in the second or third trimester of pregnancy. Ninety-seven percent aborted successfully. In 84 percent uterine contents were expelled completely. The average mean time to abortion was 10.9 hours.

It has been observed in many studies that there are no significant alterations in either the coagulation or fibrinolytic systems attributable to the use of prostaglandins. This is an important consideration in the management of intrauterine fetal death since the patient with prolonged retention is at risk for a chronic consumptive coagulopathy.

The use of prostaglandin E_2 suppositories in the management of intrauterine death seems to have convincing therapeutic advantages. The ease of administration permits initiation of therapy as soon as the diagnosis is confirmed. Most important it appears to be far more efficacious than oxytocin.

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Detrusor Dyssynergia

DETRUSOR DYSSYNERGIA has recently emerged as a well-defined clinical syndrome of vesical dysfunction, the second most common cause of urinary incontinence in the female. This is a chronic, painless, urgency-frequency type of incontinence that results from sudden uninhibited detrusor muscle activity, often triggered by a changing position, arising from bed, running or other daytime physical activity. Patients are frequently seized with an urgent desire to void, but do not always make it to the bathroom in time. The reason for the hyperirritable state of the detrusor muscle is not well understood, but in many patients this seems to be a psychosomatic and functional disorder, perhaps similar to the irritable or spastic colon syndrome.

Before there was a general awareness of the existence of this syndrome, many patients with dyssynergia were classified as having "urgency incontinence" or "true stress incontinence." It is now recognized that the urgency with detrusor dyssynergia is a motor type of urgency that occurs when the detrusor muscle contracts on a partially filled bladder. This gives a pressure discomfort that differs from the painful sensory type of urgency characteristic of inflammation or infections of the lower urinary tract.

It is even more important to differentiate detrusor dyssynergia from true anatomic stress incontinence since surgical operations designed to strengthen the defective supports of the vesical neck, as found in true stress incontinence, will not alleviate but often aggravate the symptoms of the unstable bladder. The most valuable guide to a correct diagnosis is a careful history to elicit in detail the characteristics of the urinary incontinence. With dyssynergia, physical stress acts only as the trigger mechanism to stimulate the hyperirritable detrusor. The involuntary loss of urine occurs ten or more seconds later, usually in larger amounts and over a longer interval of time as compared with true stress incontinence.

Direct electronic urethrocystometry has been a valuable aid in establishing the syndrome of dyssynergia, but it is not readily available for clinical diagnosis. Simple water manometer and carbon dioxide cystometrograms are alternative methods for clinical evaluation of bladder volume and pressure changes relative to physical stress and to filling of the bladder. A routine cystometrogram will permit recognition of the abnormal detrusor activity typical of dyssynergia.

Management of patients with detrusor dyssynergia is frequently difficult, and the results are not always satisfactory. The administration of anticholinergic drugs to decrease the uninhibited contractions of the detrusor muscle has proved beneficial in many cases. Administration of Pro-Banthine® (propantheline bromide), 15 mg three or four time per day, or Ditropan® (oxybutynin chloride), 5 mg two or three times per day, is recommended. Patients are often encouraged to consciously attempt to prolong the interval between voiding while using the anticholinergic medication. The bladder can some-

times be retrained to hold larger volumes, and the feeling of urgency may diminish.

Finally, it is most important to remember that attempts at surgical repair in patients who have no defect in the anatomic support of the vesical neck are ill-advised and invariably make the condition worse.

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Artificial Donor Insemination

ARTIFICIAL DONOR INSEMINATION is an accepted method for treating infertility when a husband is azospermic or has a low sperm count that does not respond to urologic treatment. Many couples prefer artificial donor insemination to the alternative of adoption because the wife will experience a pregnancy and will make her genetic contribution to the child. It is estimated that there are several hundred thousand persons who were conceived by donor insemination.

Careful selection of donors is essential to ensure that they are healthy, intelligent and have no history of genetic defects. The semen must have high spermatozoa counts and motility; must have few abnormalities and, if frozen samples are to be used, must respond well to freezing and thawing. The physical characteristics of the donors and their blood groups are recorded for matching with the recipient's husband.

Success of artificial insemination depends on the wife's reproductive ability, and on the accurate timing of ovulation. The three points to be established as normal are ovulation, patency of the fallopian tubes and receptiveness of the cervical mucus. Ovulation can best be determined by a premenstrual endometrial biopsy, or a plasma progesterone measurement in the midsecretory phase. Insufflation of carbon dioxide will establish the patency of at least one fallopian tube, but more accurate information can be obtained with a hysterosalpingogram done before ovulation. Laparoscopy generally is reserved for patients with a suspected tubal abnormality. The receptiveness of the cervical mucus can be determined by a slide test with donor semen. While these tests are being done, the timing of ovulation can be established by keeping a basal body temperature chart, and repeated examinations of the cervical mucus.

It is advisable to tell the husband and wife that artificial insemination is not an easy or instant way of achieving a pregnancy, and that they should prepare for a program lasting six months. During that time, if the wife is reproductively normal, she has a 70 to 75 percent chance of becoming pregnant.

When pregnancy does not occur, though the wife is apparently normal and artificial insemination is coinciding with ovulation, other causes of failure should be considered. It is possible for an ovum to be fertilized but fail to implant due to immunological rejection, or insufficient progesterone production. Recently in our laboratory, incompatibility between the husband's semen and donor's spermatozoa was detected. Results were improved by advising the couple to refrain from sexual intercourse, or for the husband to use a condom, for two days before insemination.

Artificial insemination requires careful selection of donors, evaluation of the wife's reproductive ability, ovulation timing and a psychological preparedness on the part of the husband to accept the child as his own. Despite these problems, artificial insemination is the only satisfactory method for many couples to achieve a pregnancy.

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Premature Labor

PREMATURE LABOR, before 37 weeks' gestation, and delivery remain the most significant contributors to perinatal morbidity and mortality. The cause is multifactorial. The more common predisposing or inciting conditions are urinary tract infections (especially pyelonephritis), chorioamnionitis, overdistension of the uterus (hydramnios, multiple gestations), uterocervical abnormalities (incompetent cervix, uterine anomalies), premature rupture of the membranes and placental accidents.

Suspicion of premature labor because of a history of uterine contractions can be confirmed by palpation by an experienced examiner or external fetal monitoring. Documentation of

cervical effacement or dilatation establishes the situation as an emergency requiring immediate admission to hospital and intensive evaluation and aggressive management.

The essential first step in optimal management of premature labor is prevention. Appropriate treatment of urinary infections, overdistension of the uterus, incompetent cervix, uterine anomalies and placental accidents significantly reduces the likelihood of subsequent premature labor. If prophylaxis fails or is not possible because the gravida presents laboring, the physician must answer at least three questions: (1) Is there an identifiable reason for her labor? (2) If not and uterine suppression with ethanol or one of the beta mimetic compounds is considered, can the side effects or complications of this treatment modality be avoided or managed? (3) If aggressive management of premature labor fails, can the nursery optimally care for the premature newborn?

Uncertainty in answering these questions should strongly suggest transfer of the mother to a center better able to provide aggressive treatment for the mother or, if unsuccessful, for the newborn.

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The Surgical Staging and Treatment of Ovarian Carcinoma

THE MODIFIED STAGING for ovarian cancer adopted by the International Federation of Gynecology and Obstetrics (FIGO) in January 1975 is based on findings at abdominal exploration (Table 1). This furnishes an accurate grouping of patients with similar prognoses, provided the physician conducts a meticulous preoperative and intraoperative search for metastases and records all information required to place a patient in a particular stage and substage.

In cases of abnormal supraclavicular, axillary or inguinal nodes, biopsy is required. If pleural effusion is shown to be present, this necessitates thoracentesis to obtain fluid for cytologic examination.

Abdominal exploration begins with the sampling of ascitic fluid for cytologic evaluation. If no ascites is present, separate washings are taken from the pelvis, the paracolic gutters and the undersurface of the diaphragm. The omentum, diaphragm, liver and pelvic and periaortic lymph nodes are inspected carefully and multiple biopsy specimens are taken to uncover occult metastases. An examination of the colon, stomach and pancreas is made to exclude these organs as site of a primary cancer.

Maximal reduction of tumor volume is indicated without resorting to radical operation or multiple bowel resections. Total abdominal hysterectomy, bilateral salpingo-oophorectomy and

TABLE 1.—*Federation of Gynecology and Obstetrics' Staging for Primary Ovarian Carcinoma*

STAGE I
Growth limited to the ovaries

Stage Ia
Growth limited to one ovary; no ascites
1. No tumor on the external surface; capsule intact
2. Tumor present on the external surface or capsule ruptured, or both

Stage 1b
Growth limited to both ovaries; no ascites
1. No tumor on the external surface; capsule intact
2. Tumor present on the external surface or capsule(s) ruptured, or both

Stage Ic
Tumor either Stage Ia or Stage 1b, but with ascites* present or positive peritoneal washings

STAGE II
Growth involving one or both ovaries with pelvic extension

Stage IIa
Extension or metastases, or both, to the uterus or tubes, or both

Stage IIb
Extension to other pelvic tissues

Stage IIc
Tumor either Stage IIa or Stage IIb, but with ascites* present or positive peritoneal washings

STAGE III
Growth involving one or both ovaries with intraperitoneal metastases outside the pelvis or positive retroperitoneal nodes, or both
Tumor limited to the true pelvis with histologically proven malignant extension to small bowel or omentum

STAGE IV
Growth involving one or both ovaries with distant metastases. If pleural effusion is present there must be positive cytology to allot a case to Stage IV

SPECIAL CATEGORY
Parenchymal liver metastases equals Stage IV
Unexplored cases which are thought to be ovarian carcinoma

*Ascites is peritoneal effusion which in the opinion of the surgeon is pathologic and/or clearly exceeds normal amounts.

omentectomy generally may be accomplished with persistence. All residual lesions then should be surveyed as to size and location and these data recorded for future reference.

Decreased rates of survival have been shown for each increase in stage and substage. The volume of residual tumor histologic cell type and grade of tumor also affect prognosis. An accurate assessment of prognosis as well as subsequent treatment planning demand a systematic and thorough approach to patients at the time of laparotomy for ovarian carcinoma.

SAMUEL C. BALLON, MD

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Diabetes Mellitus in Pregnancy

CAREFUL MANAGEMENT of the pregnancy complicated by overt diabetes mellitus can yield an overall perinatal mortality only two to three times higher than that of the general population. Approximately half of these losses result from sudden and, as yet, unexplained intrauterine deaths in the third trimester. These intrauterine deaths appear to be more common in women with vascular disease. Attempts to avoid this tragedy through early intervention have led to neonatal mortality from complications of prematurity. Infants of diabetic mothers may succumb to fatal congenital anomalies, with cardiac malformations particularly common. Traumatic delivery also has caused fatalities.

A diabetic woman most often will have a successful pregnancy if her care is directed by an experienced medical team. Each member—the obstetrician, internist, pediatrician, nurse and dietitian—must pay careful attention to detail. Evidence is accumulating that normalization of fetal carbohydrate homeostasis *in utero* will decrease perinatal mortality and morbidity. Diet alone or in combination with insulin therapy must be used to achieve this goal. Orally given hypoglycemic agents should not be used.

Patients should be examined as early in pregnancy as possible. A detailed obstetrical and menstrual history must be obtained and uterine size carefully assessed. Many clinicians have found it valuable to admit a pregnant diabetic patient to hospital when she is first seen. Intense instructions on diet and insulin should be given. A baseline creatinine clearance, urine culture, ultrasound, electrocardiogram and ophthalmologic consultation also should be obtained. Patients then are followed at weekly intervals.

Timing of delivery remains a controversial issue. Many large centers have reported success in delaying delivery until fetal pulmonary maturity can be achieved, by maintaining an intensive antepartum surveillance. This program should be initiated no later than 34 weeks' gestation and may require admission to hospital. Patients must be kept in good diabetic control and should have a set program of prescribed bed rest. Fetal well-being can be assessed with daily 24-hour studies of urinary estriols. Unless the assays are done meticulously and are available daily, fetal distress will be missed. A weekly contraction stress test is a valuable technique for assessing fetal condition when used by itself or in association with estriol determinations. A negative test result may enable the obstetrician to delay unnecessary premature intervention. Although the contraction stress test is done weekly, decreased fetal activity or deterioration of the patient's diabetic control may necessitate more frequent examinations. The physician should seek delivery in diabetic patients at 37 to 38 weeks' gestational age, and after the lecithin to sphingomyelin ratio has reached 2.

Nevertheless, the timing of delivery must be individually selected for each patient. Deciding when a delivery occurs in a patient is much more important than the method used. Serial inductions should be avoided and a liberal policy of cesarean section employed.

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Menopause

ALTHOUGH continual review, research and reassessment characterize part of the methodology of medical progress no single aspect of practice must meet greater challenges than those faced by estrogen therapy of menopause. These challenges demand that three questions be answered: (1) What adverse changes occur concurrent with and subsequent to estrogen deficiency and the cessation of menstrual flow? (2) Which of these are corrected by current therapy? (3) What are the dangers of this treatment? By answering these

questions sequentially we may arrive at a rational and current approach to therapy of the menopause.

1. Vasomotor instability, atrophy of urogenital structures, osteoporosis and increased emotional lability all characterize the climacteric. An unequivocal relationship between estrogen deficiency and the latter two conditions has not yet been proven.

2. Vasomotor instability occurs in 30 to 75 percent of postmenopausal women and usually persists for 1 to 3 years. This symptom usually responds well to estrogen replacement. Atrophic vaginitis and urethritis, loss of tone of breasts and diminished pelvic support all improve with estrogen replacement. Osteoporosis may be delayed and possibly prevented by estrogen therapy. However, preexisting osteoporosis cannot be reversed. The synergistic effect of exercise and proper diet upon the prevention and limitation of osteoporosis cannot be overemphasized. Indeed, these factors may be more important than estrogen treatment. Improvement in well-being and reduction of emotional lability by estrogen treatment might occur but these symptoms are too intangible to quantitate definitively.

3. A causal relationship between both breast and endometrial malignancy and estrogen treatment of postmenopausal women has long been suspected. Recently, a number of retrospective case control studies have indicated a substantially increased risk for the development of both invasive and noninvasive endometrial cancer among women receiving estrogen therapy. Additionally, a dose-response relationship and a duration-response relationship have been shown. Although retrospective studies suffer from a number of deficiencies, these reports cannot be ignored. Similar studies for breast cancer are less convincing.

With this background, it seems logical that only those menopausal patients suffering from vasomotor symptoms and those with atrophic changes should receive estrogen replacement therapy. Young women in whom bilateral oophorectomy has been done also may be candidates for treatment to prevent osteoporosis. Treatment should be intermittent rather than continuous. The periodic administration of progestins in order to differentiate or slough (or both) the estrogen-stimulated endometrium is worth considering although no studies have shown a protective effect. After one to two years of therapy, administration of estrogens should be discontinued and the need for further treatment assessed. Finally, estrogen treatment is designed to replace endogenous secretion. Pharmacological levels of hormones are to be avoided. A recently modified assay for corticosteroid binding globulin-binding capacity may provide the needed indicator which will allow us to stay within physiological dosages.

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Habitual Abortion

IN A WOMAN who has had three consecutive early spontaneous abortions a comprehensive medical evaluation should be done, followed by specific treatment or reassurance, and continued support before and during subsequent pregnancy. Contraception is recommended until the evaluation is completed. The adequacy of the luteal phase is ascertained by basal body temperature and by endometrial biopsy and serum progesterone studies on the seventh postovulatory day. An apparent defect should be documented in at least one further cycle and the underlying cause further investigated by assessing the adequacy of preovulatory estrogen stimulation.

Deficiency of estrogen effect should be treated by supplementary estrogen from the seventh day until the midluteal phase. Luteal phase insufficiency can be treated by either clomid or gonadotropin stimulation of follicular development, by human chronic gonadotropin stimulation of luteinization or by progesterone substitution during the luteal phase. The effect of treatment should be verified by repeat endometrial biopsy. A culture for T mycoplasma is sent to the virology laboratory and if positive both partners are treated with a ten-day course of doxycycline followed by repeated cultures. The endometrial cavity is evaluated by hysterosalpingogram or, preferably, by hysteroscopy. In addition to identifying uterine anomalies and submucus myomata, which are infrequent causes of early fetal loss, endometrial scarring or denudation resulting from repeated curettage may be directly visualized and treated.

Finally, a banding chromosome analysis is done on both partners. Although more costly,

consistent identification of balanced translocations requires this technique. Genetic counseling should be provided for the 5 to 10 percent of couples for whom etiologic determinants are discovered. Identification of a genetic cause is particularly important, because a subsequent pregnancy may result in the birth of an abnormal viable infant.

Those couples in whom there are negative findings on complete examination or a treatable cause is found should be reassured and offered continuing support in an attempt to avoid perpetuation of failure due to psychosomatic factors.

DAVID MELDRUM, MD

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CORRECTION

The epitome entitled "Grey Scale Ultrasonographic Differentiation of Medical and Surgical Jaundice," which appeared in the March issue on page 219, was incorrectly credited to Gabriel Wilson, MD. The author was in fact W. Fred Sample, MD.

EDITORIALS

Human Rights, Human Biology and the Egalitarian Fallacy

ONE SENSES a stirring of something profound and magnificent in the new focus on human rights in American foreign policy and the quick support it received from the United Kingdom. In these columns we have suggested that America is in the process of putting aside its ethic of materialism and replacing it with a new emphasis on a new humanism which places the individual person at the center of the stage. The changes are occurring rapidly—at an almost revolutionary pace. It even seems possible that history will record the new insistence on human rights in American foreign policy as another "shot heard round the world."

But be this as it may, human rights are very much in the public consciousness in America today. Our concept of human rights appears to derive from the Declaration of Independence which states that "all Men are created equal, that they are endowed by their Creator with certain unalienable Rights, that among these are Life, Liberty, and the Pursuit of Happiness . . . ." The essential ingredients are equality and rights and what is meant by "Life, Liberty, and the Pursuit of Happiness."

There is reason to believe that the signers of the Declaration wished to say that all men are created equal for purposes of equal justice under law and for each to have equal opportunity to life, liberty and pursuit of happiness. But now "created equal" is beginning to have wider implications. Equal rights are being applied to many other things and further, equal rights are coming to be considered equal entitlements—equal rights and equal entitlements to such things as housing, income, education, health and health care, and even to a certain freedom from risk—things which in turn seem to be becoming equated with the concept of life, liberty and pursuit of happiness.

It is suggested that this progression of "created equal" to today's egalitarianism with all of its equal entitlements involves a fundamental change in meaning which runs counter to reality and must therefore prove to be unworkable. The basic and inescapable reason for this is a biological one. It is a fact that each person is unique and different from every other person. Each person differs genetically, experientially and in individual purposes and goals in life. These are not and cannot ever be the same for everyone or for humanity. This is the fallacious assumption of today's egalitarianism. The idea that everyone is born equal and therefore should have exactly the same things in life as everyone else is a fallacy. Yet it is a fallacy that we are now trying our best as a nation to legislate and to regulate into reality. Our programs to try to do this have been massive. They are failing as they must inevitably fail, and the lesson is proving to be costly in proportion to the strength of our futile efforts.

This egalitarianism is not the wave of the future for a relatively affluent society. The new humanism *is*—the humanism that places the individual person at the center of the stage, and seeks individual personal fulfillment within the framework of the closed biosphere as the goal. Somehow the new humanism, so pregnant with potential for America to once more show the way, must be purged of this egalitarian fallacy before it is consumed by it. It is time that human nature and the nature of human society be recognized as the biological things they are. Medicine should embrace the emerging science of human biology and profess it to the nation and to the world.

—MSMW

Acute Nonlymphoblastic Leukemia in Adults

Where Do We Go from Here?

THE TREATMENT of adult nonlymphoblastic leukemia—acute myelogenous leukemia and its variants (AML)—has improved greatly in the last decade. Except for patients over 65 or 70, most physicians no longer debate the merits of therapy for this disease. This improvement in treatment has resulted in a large measure from the introduction of two new drugs into combination regimens, namely cytosine arabinoside, and daunorubricin.

The article by Embury and his co-workers, in this issue of the WESTERN JOURNAL, not only shows, as has been previously recorded, that complete remissions in the order of 60 percent may be obtained, but also addresses the important issue of the value of continued therapy once remission is obtained. The regimen employed here for remission induction involves the use of daunorubricin, thioguanine and cytosine arabinoside, one of several induction programs that have been described in recent years.[1,2] Unfortunately, all of these treatment programs must be pushed to produce marrow hypoplasia, if a complete remission is to be obtained. Therefore, as a consequence of the leukemia or treatment-induced granulocytopenia, sepsis is a common complication during remission induction, and optimum treatment of AML requires an experienced team with expertise in chemotherapy, infectious disease and total supportive care.

The major thrust of recent therapeutic studies in AML has been an attempt to prolong the precious remissions obtained only after weeks of hospital stay and careful management. Unfortunately, most of these studies have not in a controlled manner assessed the value of these "maintenance" regimens, some of which are toxic and inconvenient to administer. The study by Embury and associates clearly shows the value of a relatively safe, convenient, two-day-a-month maintenance program in prolonging remission duration. Findings in other uncontrolled studies using more intensive treatment have also suggested the value of continued therapy after induction of complete remission.[2-5] The use of immunotherapy, especially with bacille Calmette Guérin (BCG) and allogenic leukemia cells, has also been investigated as a means of prolonging the length of remission. While early results seemed favorable, longer follow-up studies have cast doubt on the value of these forms of immunotherapy.[6]

Where do we go from here? Clearly, the present drug programs, while effective, could be improved upon by the development of more "selective" agents, that is, drugs that affect leukemia cells without damaging normal marrow stem cells. At present, drugs—such as prednisone, vincristine and asparaginase—that cause complete remissions in acute lymphoblastic leukemia without the necessity of marrow hypoplasia are essentially ineffective in AML. Until such selective drugs are developed, the dilemma that we as physicians face in the treatment of this disease is that remission induction is difficult and hazardous; once achieved, we would like the patient to return to as normal a life-style as possible. Continued, aggressive treatments, if too toxic and difficult, may negate any benefits of complete remission. Yet the increased survival and remission duration noted in patients treated in this and other regimens, as well as the limited value of reinduction once relapse occurs, may justify this approach. Perhaps we should abandon the concept of "maintenance" and treat with continued cycles of effective agents, for a limited time, and to a reasonable degree of toxicity, much like the combination chemotherapy programs for Hodgkin disease and diffuse histiocytic lymphoma. The challenge here is finding even more effective and safe combinations of drugs. The finding of the present study, that splenomegaly negates the value of maintenance therapy, suggests that attempts to decrease spleen size by surgical operation or radiation therapy, after remission induction, may be worth pursuing. Continued investigation of marrow transplantation as well as additional immunotherapeutic approaches are also warranted, and preliminary encouraging reports using neuraminidase treated cells and methanol extracted residue of BCG (MER) have been reported.

A ray of hope from these and other studies, including that of Embury and co-workers, using continuous treatment programs is the small percentage of patients (5 to 20 percent) in whom complete remission lasting two years or longer is achieved.[2,3] However, acute leukemia in adults continues to be a disease with a dismal eventual outcome. Patients should be referred to physicians and centers where they can be optimally

treated in programs in which questions are asked that eventually will improve our ability to deal with this disease.

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The Slaughter of the Sacred Cows

IN THIS ISSUE of the WESTERN JOURNAL is published a conference on the management, both medical and surgical, of peptic ulcer disease. In it the gastrointestinal group at the University of California, Los Angeles, has wreaked havoc with long-standing principles which have guided therapy of ulcer disease. The proceedings of the conference are invaluable, since standard attitudes and practices have been challenged and these challenges have been supported with data.

We are accustomed to thinking that the principles of treatment of this disease—dietotherapy, antacids and anticholinergics—are secure. Evidence is now presented by this group that casts serious doubt on the efficacy of each component of the program. First, there is dietotherapy. It had long been appreciated, of course, that "bland foods of the infant variety as well as milk or milk and cream" have no noteworthy power to neutralize acid.[1,2] Present data indicate that the stimulating effect on the antral phase of gastric secretion of such food is about the same as for any other food. Further, hospital studies in Iowa a few years ago indicated no difference in the rate of healing of duodenal ulcers between a group of patients that had normal diet and a test group given the classical frequent feedings of milk, cream, cereals and so forth.[3] Yet, the effect of instituting frequent feedings of baby-type food with milk or milk and cream every hour or two hours seems to work magic in many patients. We have wondered: Is it really psychotherapy? The patient seems in this situation to be reduced to early childhood or even infancy, to be cared for by being offered something to eat frequently and to be ingesting only those foods most obviously identified with infancy. Perhaps "mothering" is better treatment than temporary acid neutralization! As noted, rate of healing of ulcers seems independent of diet. Certain substances, however, should not be drunk by patients with ulcer disease during periods of activity of their disease; namely coffee and alcohol.[4] These drinks stimulate gastric acid greatly and, although neutralizing acid in treatment of peptic ulcer seems less important than formerly (see below), to facilitate high secretion makes little sense. Aspirin also should be forbidden. Although other drugs have been claimed to be ulcerogenic, particularly steroids, the evidence that they are harmful is not clear.[5]

The mainstay of medical therapy remains antacids, particularly when prescribed to be taken one hour after meals. Most commonly, this means an aluminum hydroxide-magnesium containing compound. In liquid form antacids have different acid neutralizing potencies, 30 to 60 ml of the more potent ones being active for three to four hours. They are commonly believed to be useful; that is, their prescription is associated with pain relief, followed by ulcer healing. However, we now learn from "Treatment of Peptic Ulcer Disease," in this issue, that neutralizing acid in ulcer disease may not be necessary for either pain relief or healing. The authors report that findings of recent double-blind studies testing these powers in ulcer patients indicate that antacids may have no therapeutic potency. Pain relief is no better than placebo; further, one study of endoscopic examinations of patients during treatment with antacid or placebo reports that the rate of healing in gastric ulcers is approximately the same. We must note that another study reported more rapid healing of gastric ulcers treated with antacids. Whether these agents accelerate healing of duodenal ulcers is still unsettled. The question may be answered by controlled trials with the dose regimen shown by Fordtran to produce optimal intragastric neutralization.[4] There is no evidence that adequate neutralization was produced in earlier studies. Calcium carbonate is an effective neutralizer of acid, but it has the disadvantages of promoting an acid rebound via gastrin release

following acid neutralization and possible hypercalcemia.

Anticholinergics are still used in the treatment of ulcer disease. The rationale is the reduction of acidity through vagal blockade. The well-known undesirable side effects of these drugs have reduced their attractiveness—bladder atony, constipation, annoying xerostomia, blurring of vision, tachycardia and so on. Some of these side effects can be dangerous in people with underlying serious disease of one or more of these target organs. There is no doubt that these preparations significantly reduce acid secretion.[4] Again, one asks: Do they alter pain and do they accelerate healing? Many of the studies which have been done purporting to show the efficacy of these drugs fall short of the mark either because the preparations were not given in sufficient amounts to inhibit acid secretion or they were not double-blind studies. The lack of potency is further illustrated by failure in adequately controlled studies to show that such preparations reduce the frequency of recurrence of the disease. Their best use would seem to be administration at bed time, particularly for patients with pronounced hypersecretion or for those with nocturnal pain.

Admission to hospital for treatment of most patients with ulcer disease, particularly gastric ulcers, is no longer held important. The report by the UCLA group indicates that little or nothing is to be gained from treatment of patients with gastric ulcers in hospital. The same is true for duodenal ulcers, uncomplicated by perforation, bleeding or obstruction. Whether or not abstinence from smoking is indicated in the treatment of the disease is also questionable. However, as the authors rightly point out, smoking should be interdicted in all patients, healthy and otherwise.

The UCLA discussion on surgical operation for peptic ulcer is a fascinating analysis. The indications for operation are clearly set forth and special attention must be paid to the category which heretofore has been called the "intractable ulcer patient." Many of those who have much experience in the field maintain that surgical therapy for ulcer disease, no matter which form of operation is used, has its poorest results in patients for whom the indication for operation is least compelling. Among this group stand prominently those whose disease has been called intractable.

Dr. Grossman rightly questions the use of the term intractability; he appears convinced that medical treatment, in whatever form one chooses, may well not alter the natural history of the disease. I do not agree. I believe (without data) that the doctor-patient relationship has a positive influence on the course of duodenal ulcers. The prescription of medications is a link between the doctor and the patient. It is perhaps not the pharmacological potency of the various preparations that does the trick; rather, it is the as yet unexplained magic of the physician. The course of the disease in many patients is a relentless march to "intractability" because it has not been influenced by a sympathetic, informed and interested physician.

Dr. Meyer in the conference reports a difference in results of operation in ulcer disease between Veterans Administration hospital and private practice populations,[6,7] the former group suffering poor health after all procedures. Perhaps socioeconomic factors influence the result; but the personality of the patients may also be crucial. Alcoholism and poor work records are as commonly associated with noncompliance with medical management before operation as they are with dismal results of operations. This group is not interacting as well with physicians as are middle and upper-middle class private patients. It may be that this group's socioeconomically-determined adaptation to medical and surgical modes of therapy is identical. It would be interesting to compare the records of preoperative attendance in clinics and compliance with management of these groups which differ so strikingly postoperatively. The question might be answered by a properly designed clinical study.

Granted surgical operation is indicated (by whatever set of criteria of severity or intractability), what are the best procedures? Surgeons have moved steadily away from the more mutilating operations. Results seem to indicate that, although we are paying a price for higher recurrence of ulcer disease, the crippling effects of more extensive procedures have been significantly lessened. There are several aspects to this problem of choice of operation which are fascinating and require further study. The first of these is the relationship between recurrence of ulcers and acid secretion. The incidence of recurrent ulcers with selective vagotomy and pyloroplasty is higher than following subtotal resection and truncal vagotomy or subtotal resection and selective vagotomy.[6] Is it correlated with higher acid secretion? If it is not, what are the reasons for the higher recurrence rate? It seems clear that vagotomy and pyloro-

plasty are indicated for those in the "intractable" category, particularly if severity of disease is difficult to judge and for those in whom there is a gross personality disorder or alcoholism. Perhaps the superselective (parietal cell) vagotomy will be *the* operation in this group as well as for those who bleed repeatedly from duodenal ulcer.[8] The higher incidence of rebleeding in patients with duodenal ulcer disease who have had subtotal gastrectomy and vagotomy for bleeding duodenal ulcer than in those who have had vagotomy and drainage requires further investigation.

The review is of great interest also because it discusses other agents, such as H-2 blockers, that may become *the* only medical treatment of ulcer disease. Will use of cimetidine cure ulcers and prevent recurrences? The final test of the acid-ulcer thesis is at hand. The UCLA group tells us that early trials show a remarkable inhibition of acid secretion following administration of this drug and there are reports of successful management of severe peptic ulcers.[9] Is an escape from the blockade possible? What about compliance and long-term toxicity?

This report by the UCLA group also stimulates us to think about pathogenesis of peptic ulcer, particularly duodenal ulcer, disease. We are still ignorant of its pathogenesis. The pharmacological basis for therapy with currently available drugs is questioned. We still do not understand the ingredients of "good patient care," and we have not scratched the surface of our understanding of the psychological makeup of patients—which may doom much of present medical treatment to failure. Finally, the conference reviews the status of surgical procedures and gives hope that the most minimal types of intervention may yield the most success. We await the brave new era of treatment with powerful drugs which will reduce both acid and the need for any surgical operation—granted patient compliance and absence of toxicity.[10]

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The Saccharin Affair

THERE ARE MANY PHYSICIANS who may question the wisdom of the recent action by the Food and Drug Administration (FDA) to ban the use of saccharin as a food additive because of evidence that it may cause cancer in rodents. Saccharin has been a useful adjunct in patient care for more than 40 years and has not yet been associated with the development of cancer in humans. From a physician's standpoint, it would seem that a decision whether or not to ban saccharin should be based on a weighing of its benefits against the possible dangers of its use, or the undesirable effects of banning its use. Many physicians would say that on such a balance the benefits of allowing the use of saccharin prevail over the possible but as yet unproved dangers.

A first impulse is to blame the action by the FDA on a skittish federal bureaucracy that is unwilling to assume any responsibility for any possibility, no matter how remote, of any citizen ever getting cancer from ingesting saccharin. But this is not the case. The Congress has mandated the decision, in advance of the evidence and without weighing the pros and cons. The Congress decided quite simply that any substance that has ever been shown to cause cancer in animals must be banned from use as a food additive. It passed a law. The FDA has to comply.

But the question may be asked whether the best interests of citizens are really being served and whether more harm than good is being done. Perhaps there are some things that *are* best left to doctors.

—MSMW

CASE REPORTS

Refer to: Lee C, Nagel EL: Abnormal sensitivity to succinylcholine —A possible obstacle to nerve repair. West J Med 126: 310-313, Apr 1977

Abnormal Sensitivity to Succinylcholine

A Possible Obstacle to Nerve Repair

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IN THE SURGICAL EXPLORATION and repair of severed peripheral nerves, and operations near other nerves (for example, facial), a prolonged neuromuscular block is undesirable because elicited muscle response serves as a guide for positive identification of the nerve. In these circumstances, continuous or prolonged neuromuscular block is ordinarily avoided by the anesthesiologist although use of a single dose of succinylcholine for a brief period of paralysis to facilitate intubation of the trachea is a common practice.

The anesthetic complication of rare, unexpected and prolonged neuromuscular block resulting from a single dose of succinylcholine[1] occurring under these circumstances may produce problems if not recognized. This report emphasizes the need for awareness of this possibility by anesthesiologists and surgeons.

Report of a Case

A 34-year-old man was admitted to the operating room for exploration and possible grafting of the severed left radial nerve under general anesthesia. This injury was a result of multiple stab wounds to the left arm six weeks before admission and the nerve was completely severed at several locations. Primary repair of the wounds was accomplished under axillary block at the time of original injury without incident. The patient's medical history included an apparently uneventful tonsillectomy and adenoidectomy as a child. There was no personal or family history of anesthetic difficulties. Physical and laboratory examinations showed no abnormalities except for the present illness. He was classified an ASA I anesthetic risk. He weighed 70 kg and was 170 cm tall. He was taking no medication that might affect the action of the neuromuscular blocking agents.

Premedication consisted of meperidine, 100 mg, and atropine, 0.4 mg given intramuscularly one hour before induction of anesthesia. On establishment of an intravenous infusion, another 100 mg of meperidine was injected in divided doses. Satisfactory sedation followed. Sleep was induced with thiopental, 300 mg in divided doses. Succinylcholine, 80 mg, was injected intravenously to facilitate intubation of the trachea. Following transient fasciculation, profound relaxation occurred. Anesthesia was maintained with 60 percent nitrous oxide with oxygen. The plan was to titrate additional doses of thiopental and meperidine as needed for the maintenance of anesthesia, with continuous neuromuscular block being avoided. Because of the use of potent respiratory depressants, no attempt was made to let the patient breathe spontaneously, nor was an effort made to see when he recovered from the single dose of succinylcholine he received during induction of anesthesia. Instead, purposeful hyperventilation was instituted manually. The incision was well tolerated and there was no tachycardia, hypertension, tearing, mydriasis or other signs of inadaquate anesthesia during the operation.

Seventy minutes after induction of anesthesia, the surgeon had repeatedly failed to elicit contraction of the muscle by stimulation of several tissue structures which appeared to be the distal nerve stump. While exploration continued, the nerve stimulator being used by the surgeon was sent out for inspection to determine if it was working. Another nerve stimulator was obtained. The second nerve stimulator also failed to elicit a response.

To rule out the possibility of prolonged neuromuscular block from succinylcholine,[1] the other upper extremity was positioned for neuromuscular

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studies.[2,3] Stimulation of the ulnar nerve at the wrist with a Grass Model S4 stimulator resulted in no response of the fingers. Eighty minutes after injection of succinylcholine, there was still no twitch response to single stimulus. Tetanic volley of stimuli at 50 Hz elicited a barely perceivable tetanic contraction which faded completely. The posttetanic twitches were facilitated enough to become visible for one minute after the tetanus. The patient remained apneic with ventilation supported manually.

Another 20 minutes elapsed before the elicited thumb twitch became recordable. The neuromuscular block was characterized by fade of tetanus, fade of train-of-four, pronounced posttetanic facilitation, and slow recovery[1-4] (Figure 1, upper panel). A clinical working diagnosis of prolonged neuromuscular block resulting from administration of a single dose of succinylcholine during induction of anesthesia was established. Enflurane, a potent inhalational anesthetic was added, to avoid the possibility of inadequate anesthesia masked by profound paralysis.

A decision was made to attempt restoration of the neuromuscular transmission as soon as possible in order to permit the operation to proceed. Following 0.75 mg of atropine, 15 mg of edrophonium was injected intravenously as a test.[1,3] Immediately the force of the thumb twitch tripled. The train-of-four ratio became 0.4.[2,3] Tetanic

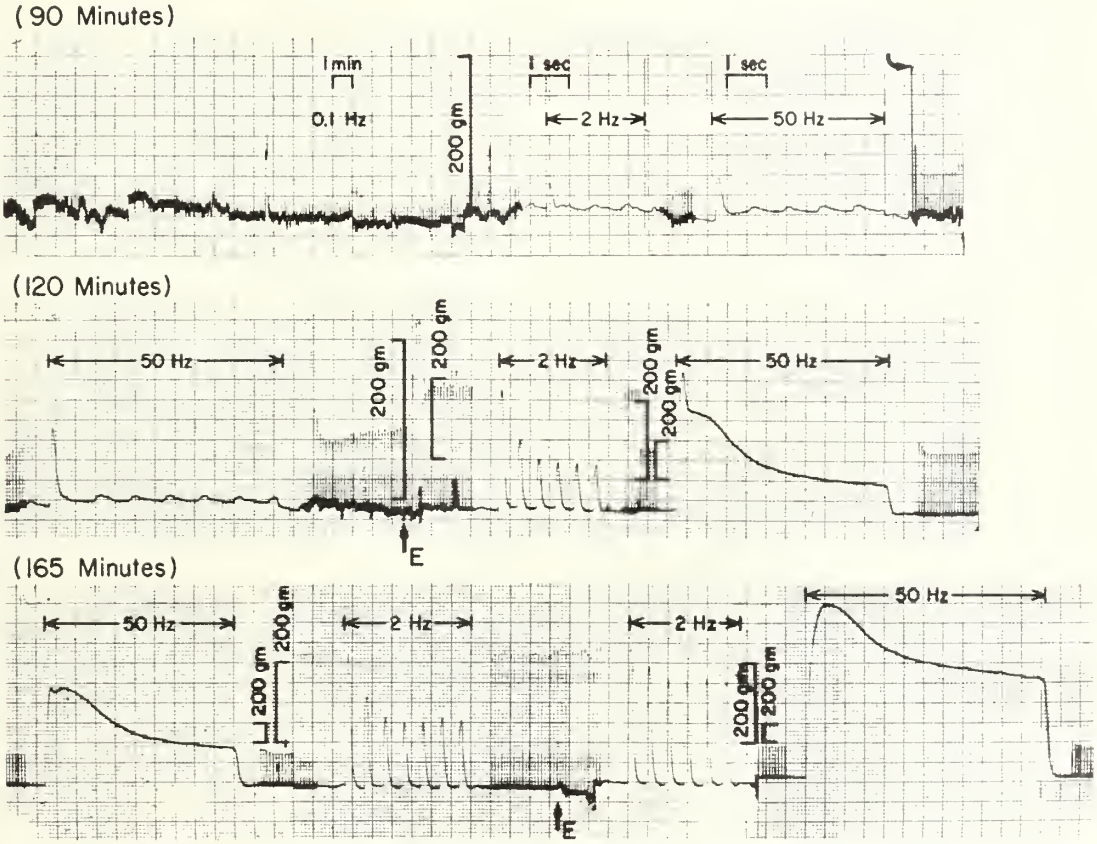

Figure 1.—Segments of record of neuromuscular study done in the case reported. The right ulnar nerve was stimulated at the wrist with 0.1 msec square pulses of supramaximal voltage. The force of adduction of the thumb was recorded via a transducer (Grass FT 10). In parentheses at the beginning of each panel is time elapsed from the injection of succinylcholine, 80 mg. Time scale represents 1 minute during twitch, 1 second during train-of-four and tetanus, as indicated. The stimuli were repeated at 0.1 Hz (twitch), 2 Hz (the beginning four responses consisting the train-of-four), or 50 Hz (tetanus) as marked. Force scale represents 200 grams throughout. The sensitivity of the recorder was changed as marked to match the force of contraction. **Upper panel:** Before injection of edrophonium. Note weak contraction, slow recovery, complete train-of-four and tetanic fade, and pronounced posttetanic facilitation. (Curved arrow marks the first posttetanic twitch). The wavy baseline was due to transmitted pulses because of high sensitivity of the recorder. **Middle panel:** Effect of edrophonium (15 mg given intravenously at E). Note immediate improvement in twitch, train-of-four and tetanus. **Lower panel:** Repeat injection of edrophonium (15 mg intravenously at E). Note no further increase in the twitch, but definite increase in the train-of-four, and the tetanic contractions.

contraction strengthened and became better sustained (Figure 1, middle panel). Spontaneous respiration returned five minutes later. The tidal volume was 300 ml and the respiratory rate 18 per minute. The improvement in muscle force persisted without return of the block to the previous level. Fifty-five minutes later, another 15 mg of edrophonium was injected. The thumb twitch did not improve further. The train-of-four ratio increased to 0.76. The tetanic contraction was also improved (Figure 1, lower panel). The tidal volume increased to 420 ml. The respiratory rate became 12 per minute. Again, the effect of edrophonium persisted.

Meanwhile, the surgeon had identified the distal nerve stump by the elicited contraction of the muscle. The gap between the stumps was measured and a nerve graft from the right sural nerve was interposed.

The remainder of the eight-hour anesthesia was uneventful. On completion of the operation, anesthesia was discontinued. The patient woke up promptly, showed no signs of neuromuscular block and was extubated.

Following discharge from the hospital, the patient could not be contacted. Arrangement was made to have plasma cholinesterase activity determined, but the advice to return to the hospital was not followed.

Discussion

A dose of 1 mg per kg of body weight of succinylcholine which normally produces a brief period of paralysis sufficient for intubation of the trachea, rather than wearing off in five to ten minutes, may in some persons produce paralysis for 30 minutes to several hours. This prolonged response may result from a quantitatively deficient or a qualitatively defective plasma cholinesterase (pseudocholinesterase), the enzyme which normally hydrolizes succinylcholine rapidly.[1]

Deficiency of the enzyme occurs in severe liver disease and following irradiation. It may also occur in patients treated with echothiophate iodide (Phospholine Iodide®),[1,5] an eye drop capable of prolonged inhibition of plasma cholinesterase. Diagnosis is based on quantitation of the plasma cholinesterase activity.

Qualitative defect of plasma cholinesterase, more commonly responsible for a prolonged response, results from a genetically determined abnormal or atypical enzyme, inherited as a somatic recessive gene.[1,6,7] Instead of two normal alleles (NN) and a typical enzyme, these persons have one or two abnormal genes which lead to production of atypical enzymes. The atypical enzymes are dibucaine-resistant,[6] fluoride-resistant or silent.[1] They are commonly denoted as DD, FF or SS, respectively, if homozygous; or ND, NF or NS, respectively, if heterozygous. Diagnosis is established by measurement of the *in vitro* percent inhibition of the enzyme activity by the inhibitors.[1,6,7] In the presence of dibucaine (10^{-5} M), the activity of the normal enzyme (NN), is inhibited by 80 percent. The dibucaine-resistant atypical enzyme is inhibited by only 20 to 30 percent, if homozygous (DD), or 50 to 60 percent if heterozygous (DN). The fluoride-resistant atypical enzyme is assayed similarly, using fluoride as the inhibitor. The percent of inhibition is called dibucaine number[1,7] or fluoride number.[1] Patients with homozygous silent gene (SS) have no plasma cholinesterase activity. The DD type atypical enzyme accounts for most of the observed cases of notably prolonged neuromuscular block following injection of a single dose of succinylcholine. The incidence has been estimated to be 1:2800.[1,7]

Although laboratory and clinical screening tests are theoretically available for identification of persons with abnormal plasma cholinesterase activity, no screening tests have gained popularity, because they are costly, time-consuming, rarely rewarded and not readily available. In addition, these enzymatic defects do not result in difficulties for the patients so long as they do not receive succinylcholine. A patient's or family's history may give a clue to the possible existence of this abnormality. Most cases, however, were recognized only after the patients had received succinylcholine and had failed to recover from the neuromuscular block promptly. Even after administration of succinylcholine, the prolonged paralysis may not be recognized if the patient is maintained on controlled ventilation, has a smooth anesthetic course, receives another neuromuscular blocking agent or undergoes a long operation during which spontaneous recovery eventually occurs. Heterozygotes present no problems and often go undiagnosed because the paralysis lasts only 10 to 30 minutes and occurs at the time when ventilation is normally controlled during the induction of anesthesia. Properly managed, patients with prolonged paralysis will eventually recover without sequelae. This case report, therefore, illustrates a special situa-

tion where the routine use of succinylcholine in order to facilitate intubation of the trachea became an obstacle to surgical operation, was inconvenient to the anesthesiologist and could be dangerous for some patients.

Clinical diagnosis and management of the prolonged paralysis resulting from abnormal sensitivity to succinylcholine can be aided by proper neuromuscular studies.[2-4] Two types of neuromuscular block are identified clinically.[1-3] Neuromuscular block by d-tubocurarine and related drugs, generally classified as nondepolarizing neuromuscular blocking agents, is characterized by onset of block without fasciculation, fade of tetanic contraction during partial block, posttetanic facilitation and antagonism ("reversal") of the block by anticholinesterases. Neuromuscular block by succinylcholine and related drugs, classified as depolarizing neuromuscular blocking agents, is characterized by fasciculation during onset of block, nonfading tetanic contraction during partial block, lack of posttetanic facilitation and enhancement of the block by anticholinesterases. Prolonged neuromuscular block by succinylcholine, in normal patients who receive excessive amount of the drug, as well as in patients with atypical plasma cholinesterase who receive a normal intubation dose of the drug, becomes characterized by signs of curare-block, with slow recovery.[2-4] Unlike neuromuscular block by d-tubocurarine, however, the block is not necessarily reversible by anticholinesterases. Attempt at reversal carries the potential risk of increasing the block.[1] Recent reports have suggested that train-of-four stimulation is valuable in confirming the changing nature of neuromuscular block by succinylcholine and in management of patients with prolonged paralysis by succinylcholine.[2-4] This we have confirmed in this patient. Test antagonism by use of edrophonium, a short-acting anticholinesterase, is advisable before long-acting anticholinesterases are tried.[1] The observation that edrophonium-antagonized neuromuscular block did not return to the previous level of block despite the short duration of its anticholinesterase activity remains to be explained.

Summary

A case of prolonged neuromuscular block resulting from administration of a usual dose of succinylcholine for intubation of the trachea is reported in a patient in whom anesthesia was induced for exploration and possible grafting of the severed radial nerve. Prolonged neuromuscular block was undesirable because it prevented elicitation of the muscle response for identification of the nerve tissue. The high degree of vigilance against rare complications and the value of communication between the surgeon and the anesthesiologist are emphasized. Cause, diagnosis and management of the abnormality are discussed.

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Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgment before publication.

More on Estrogen

To the Editor: I am a private practitioner of medicine who does not have the time or the inclination to do research or even statistical studies. However, I would still like to add my two cents worth to the postmenopausal estrogen controversy which was again presented in two separate letters to the editor by Doctors Stephen Brown and Gilbert Gordan in the February 1977 issue of the Western Journal [West J Med 126:151-155, Feb 1977]. Although I have not done any statistical analyses or investigative studies, I would like to suggest as food for thought to my investigative medical colleagues the following questions and observation:

1. Is the diagnosis of endometrial carcinoma discovered earlier in those women receiving estrogen therapy?

2. Is the outcome better in those women who have been receiving estrogen therapy?

3. It has been my unresearched observation in my small private series that 100 percent of my patients in whom ovarian carcinoma has developed have received no estrogen therapy. Conversely, I have seen no cases of ovarian carcinoma in my patients who have had long-term estrogen therapy. Is this purely chance or has this been studied and if it has not, should it not be studied? If my original observation is true then if one had one's druthers, certainly it would be better to take estrogen with the risk of endometrial carcinoma developing or at least of lighting it up than taking the risk of not preventing or at least suppressing ovarian carcinoma.

4. Since the disadvantages of estrogen therapy for menopausal women have been developed from statistical analyses, possibly statistical analyses involving all of the measurements of the effects of estrogen might demonstrate quite graphically that estrogen therapy for all or at least for carefully selected women might—both from a morbidity and mortality standpoint, in addition to patient well-being—prove to be beneficial.

5. Possibly total hysterectomy in carefully selected women might increase the benefits of estrogen therapy while eliminating some of its problems.

6. Finally, it would be extremely helpful to private practitioners if academicians and medical centers would provide the medical community as well as the lay press with not only the detriments of estrogen therapy but also its advantages and alternatives. At present, we are left in the uncomfortable position of facing patients who have thrown away their estrogen medications on the strength of the negative published reports yet return to our offices seeking other treatment, which is not available.

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Controversy Over Nursing

To the Editor: Is that fine, long marriage of the medical and nursing professions headed for the rocks? The winds of discord and discontent have been blowing here in the hills of Idaho.

There have been hints of trouble for some time, but what brought it all to the surface was a newspaper article in which a physician-member of the State Board of Education blasted our two-year nursing schools, asserting that they graduated inadequately trained students. That brought some angry cries of protest.

The Idaho Hospital Association followed with a position paper claiming, among other things, that hospitals are finding it necessary to provide extensive clinical training before these newly graduated nurses can function safely and efficiently. That added to the ill feeling.

The Idaho Medical Association and the Board of Medicine began taking a close look at the Medical Practice Act with an eye towards stricter definition and delineation of levels of practice. The revised Nurse Practice Act, as proposed by the nursing association, was scrutinized rather carefully, with a certain degree of uneasiness. Were these nurses proposing to practice medicine?

As an upshot of all this the State Board of Education decided to call in outside help. An unbiased evalution was needed. Nursing educators from California and Colorado were asked to tour the state to survey the nursing schools, and to sample the opinion of physicians, nurses, educators and interested citizens. This information would then be crystalized into concrete recommendations.

The comments were enlightening. People welcomed the opportunity to unburden themselves. Some remarks from both camps reflected a chip-on-the-shoulder attitude. Here and there a physician grumbled: "We don't get the respect we are entitled to. Remember those days when a nurse would get up when you came to her station?" And some of the nurses bristled with: "They have to get over the notion that we are handmaidens to physicians!"

On the face of it, these remarks are ludicrous. But they are basic to our present interprofessional tiff. If we are wise we will accept them as counterirritants that could hasten the healing of the wound.

Most comments were constructive. Yes, associate degree nurses need more clinical training. Perhaps they should serve an internship before being licensed. Sure, physicians should be given the opportunity to take part in the nurse training programs. Possibly the whole program should be structured so that a nurse could climb the educational ladder from licensed practical nurse (LPN), to associate degree, to clinical or three-year degree, to baccalaureate degree, with opportunities to specialize along the way. And so the comments went.

The simple fact is that most certainly nurses are no longer "handmaidens" in any sense of the word. The image of Florence Nightingale lingers, but the rapid strides of medicine, with the increasing mass of sophisticated technology, have brought new levels of expertise to nursing, new categories of nurse professionals.

We now have neonatal nurses, oncology nurses, intensive and coronary care nurses, trauma nurses, and obstetrics nurses with new skills of fetal monitoring. (Remember the day when we would allow nurses to do only rectal examinations?) And of course we still have the courageous "barefoot doctor" back in the isolated village of the Sawtooths. But now she has had specialized training, and deserves the name of "nurse practitioner."

Maybe this hubbub in the hills of Idaho is a spring thunderstorm that will clear the air. Maybe associate degree nurses just out of two years of training are, indeed, undertrained and inexperienced. Yet each of us can well remember our own ineptness as externs and interns. Ways will be found to widen the clinical experience of these fledgling nurses.

It's time physicians and nurses alike flicked the chip off our respective shoulders. Let's accept the fact that we are partners in the most rewarding task there is—patient care, *caring* for the patient. We are privileged to be in a profession that allows us to learn and to grow, even as we work.

This marriage has just everything going for it!

E. R. W. FOX, MD
Coeur d'Alene, Idaho

Miconazole in Coccidioidomycosis

TO THE EDITOR: The detailed report by Sung and co-workers [Sung JP, Grendahl JG, Levine HB: Intravenous and intrathecal miconazole therapy for systemic mycoses. West J Med 126:5-13, Jan 1977] on miconazole therapy of fungal infections was read with great interest. I would like to offer the following comments and corrections.

The article states " . . . there was no information regarding the use of intrathecal miconazole . . . " and then presents data on a case. The following information will be of interest. We earlier published[1] that four patients with fungal meningitis "received miconazole (maximum total dose 465 mg) directly into the cerebrospinal fluid (CSF) space (lumbar, cisternal, ventricular). Miconazole was well tolerated by any route. With one exception, CSF miconazole concentration after intra-CSF use (maximum dose 20 mg) was 1.4 mcg/ml after 24 hours, 0.13-0.34 mcg/ml (mean = 0.25) after 48 hours, and <0.1 mcg/ml after 72 hours."

It is incorrectly indicated that we reported rouleaux formation secondary to intravenous therapy. We reported[2] erythrocyte aggregation—I would guess this is the same phenomenon reported by

Sung and co-workers as "The plasma appeared to be saturated with oil. . . . "

Data on protein binding are attributed to Lewi and associates,[3] but there is no information relevant to binding in the reference cited. We have, however, reported plasma protein binding of 91 to 93 percent[2] by ultrafiltration and equilibrium dialysis methods.

Sung and co-workers did not find effects on marrow of miconazole, but I call your readers' attention to our documentation of reversible drug-related thrombocytosis, and anemia due to normoblastic hypoplasia.[4] The current incidence of these effects in serial observation of study patients is 30 percent and 48 percent, respectively.[5] The most important side effect of miconazole therapy to be aware of is hyponatremia, which has been severe in some patients and occurs with an incidence as high as 47 percent.[5]

I also feel it is premature to conclude that intrathecal therapy is necessary in every fungal meningitis patient treated with miconazole. Of five (of 13) patients with meningitis in our report in whom there was response to miconazole,[1] four received only intravenous therapy. In addition, Sung and associates suggest the reason for persistence of miconazole in CSF as compared with serum is binding to the vastly higher protein concentration in the latter. Of course, this phenomenon would have exactly the opposite effect, the drug bound to protein providing a reservoir for release of bioactive drug. A logical explanation for the difference is that the extrarenal metabolic pathways (presumably liver) are not encountered in the CSF space.

Finally, I believe that giving this drug by intravenous push should be discouraged, even under electrocardiographic monitoring, in the absence of animal or human data indicating this is safe. Sung and co-workers noted arrhythmias with this method, including one episode of ventricular tachycardia.

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Dr. Sung Replies

TO THE EDITOR: *Paragraph 1.* When I stated "there was no information regarding the use of intrathecal miconazole," [Sung JP, Grendahl JG, Levine HB: Intravenous and intrathecal miconazole for systemic mycoses. West J Med 126:5-13, Jan 1977] I was referring back to June 1975 when I first requested permission for the emergency use of this drug intrathecally for a critical patient (Case 4). Janssen Research and Development and the Food and Drug Administration (FDA) informed me at that time there was no available information regarding dosage schedule and safety of this therapy. They asked me to submit a dosage schedule before they would consider my request. The 20 mg dosage per intrathecal injection which I gave them was arrived at by comparing miconazole with our experiences with amphotericin-B for the treatment of disseminated coccidioidomycosis,[1] as shown in the following formula:

$$\frac{\text{Intrathecal amphotericin-B}}{\text{Intravenous amphotericin-B}} = \frac{\text{Intrathecal miconazole}}{\text{Intravenous miconazole}}$$

- The intrathecal dosage of amphotericin = 0.5 mg (varies from 0.25 to 1 mg).
- Daily intravenous amphotericin-B = 50 mg (varies from 30 to 100 mg).
- Daily intravenous miconazole = 1,800 mg (varies from 1,200 to 3,000 mg).
- The intrathecal dosage of miconazole from the above formula would be 18 mg.

Each milliliter of solution contains 10 mg of miconazole; for convenience I asked the FDA for permission to use 20 mg (2 ml) per intrathecal injection. Fortunately enough, this 20 mg dosage happened to be a safe and effective dosage despite the dissimilarity of structure and pharmacological action of the two drugs. It was six weeks after we had treated two patients with intrathecally given miconazole that the information on dosage and safety of intrathecal therapy with miconazole was given to other investigators by Janssen Research and Development. The short abstract,[2] as referred to by Dr. Stevens as their "early paper," was based upon the information of our initial clinical trial.

Paragraph 2. We did misquote their observation on erythrocyte aggregation, which is not the same as rouleaux formation.

Paragraph 3. We have no experiences in miconazole-plasma-protein binding studies. The information we referred to, that over 90 percent of

miconazole is rapidly bound by the plasma protein after intravenous infusion, was given to us by Janssen Research and Development from their research laboratory data by Lewi and co-workers.[3]

Paragraph 4. In regard to bone marrow functions, we did observe a transient alteration of the platelet count in both directions. One patient had a decreased platelet count; two patients had increased platelet counts; these values reverted to normal in subsequent studies without a change in the dosage of miconazole. Bone marrow studies in these patients revealed normal marrow without evidence of either an increase or decrease of the megakaryocyte activity. In regard to anemia, one patient had an increased hemoglobin value.[4] Two patients had no change in hemoglobin and seven patients had decreased hemoglobin values, as we stated in our recent paper.[5] However, in the last group of patients who had other concurrent illnesses, miconazole could not be indicted as the sole cause of their anemia. For this reason, we are now conducting a prospective bone marrow study in all patients referred for miconazole therapy. Dr. Stevens stated "the most important side effect of miconazole therapy is hyponatremia" occurring in 47 percent of their patients. We have not observed a single incidence of hyponatremia which can be attributed to miconazole therapy in 13 patients we have treated to date.

Paragraph 5. We have *never* stated that intrathecal therapy is necessary in *every fungal meningitis.* However, we did state that intrathecal therapy is essential for patients with positively diagnosed *coccidioidal meningitis* for reasons we have described in our paper. The same opinion was shared by the late Dr. William Winn.[6,7]

Paragraph 6. Information of the adverse cardiac effect of this drug in an animal study by Jageneau was cited by Symoens.[8] Based on this information, we conducted a careful and controlled study of this effect in humans and we found the optimum rate for infusion to be between 15 to 30 minutes. A faster rate of intravenous infusion of this drug was found to be accompanied by a dangerous and adverse cardiac effect. Therefore, we do not recommend its administration by the intravenous push method.

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Refer to: Goldberg GA, Hein LM, Rosales SM, et al: Criteria and flowsheet for utilization review by level of care (Health Care Delivery). West J Med 126:318-323, Apr 1977

Criteria and Flowsheet for Utilization Review by Level of Care

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THE CONCEPT of level of care,[1] a well established touchstone for deciding on the appropriate placement of patients in one of a number of available long-term care facilities, has more recently been recognized as a reasonable basis for deciding whether or not a patient, at any given moment, should be located in an *acute-care hospital.*[2] In epitome, the application of level of care to hospital utilization review entails determining whether or not a given patient, at a given moment, requires a level of care that can be furnished only in an acute-care hospital rather than in a facility providing less intensive care.

At the University of California, Los Angeles, Hospital and Clinics, we define level of care as "the type, number, and/or intensity of a combination of physician, skilled nursing, and ancillary services."[1] If, at any selected moment during a patient's stay, the patient requires a level of care that can be provided only in an acute-care hospital, he or she belongs in the hospital; if the services needed could be provided in a less intensive setting, the patient is said not to require an "acute hospital level of care," and is inappropriately placed in our acute-care hospital.

Although a number of acute-care hospitals (many of which employ utilization review coordinators) make use of level-of-care criteria for determining appropriate hospital placement,[3] most of the guidelines for determining level of care have been, up to this time, quite vague. The example of level-of-care criteria provided by Goran and co-workers[2] gives only the general outline of questions to be addressed by the person determining the patient's needed level of care. A physician or utilization review coordinator using this outline of so-called level-of-care criteria to review an individual patient, could be said to be approaching the problem logically, but not really explicitly. The notion of what *is* a "hospital-only" physician service, or skilled nursing service, or ancillary service (whether as to type, number or intensity) would still remain in the reviewer's head. The review therefore would be subjective, at a time when greater objectivity of review is desired.[1,4]

Explicit Level-of-Care Criteria

To remedy this situation, we developed a set of explicit level-of-care criteria, to be used as guidelines for review of UCLA utilization review coordinators (see Figure 1). We amalgamated, adapted and expanded three provisional sets of level-of-care criteria which had been developed previously by three nonacademic acute-care hospital utilization review (UR) committees in the San Francisco Bay area.[5] Our effort in no way constitutes a research project, nor does it purport to be one. It is a considered empirical step to assist our

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UCLA HOSPITALS AND CLINICS LEVEL OF CARE CRITERIA: Guidelines for Utilization Review

(The Level of Care Guidelines are representative, not all-inclusive.)

WHAT SERVICES SHOULD A PATIENT BE RECEIVING OR NEED AVAILABLE IN ORDER TO JUSTIFY ACUTE HOSPITAL LEVEL OF CARE ?

I. PHYSICIAN SERVICES

1. Specific requirement for daily visits, e.g., situations requiring physician skills to observe, evaluate, and adjust orders.
2. Examinations and orders for treatment during preoperative and other acute care periods of stay.
3. Operative and other technical procedures.

II. SKILLED NURSING SERVICES

1. Continuous availability of nurses for intermittent observation and decision-making, including, but not limited to:
   a. where patient is acutely ill such as with uncontrolled diabetes or hypertension.
   b. where complex diagnostic or therapeutic procedures are being done requiring frequent or repeated observation.
   c. where pre and postsurgical management is provided.
   d. where potentially dangerous drugs or drug combinations are being used.
2. Frequent skilled nursing services including, but not limited to:
   a. IM medications and IV therapy.
   b. inhalation therapy, pulmonary therapy, and urgent administration of oxygen.
   c. teaching management of postsurgical appliances, medication regimens, and special diets.
   d. specialized procedures, e.g., suctioning, postural drainage, compresses, frequent dressing changes.
   e. cardiac resuscitation.
   f. intensive care nursing, e.g., ICU, CCU, RCU, premature nursery.
   g. specialized nursing care, e.g., rehabilitation, dialysis.
   h. obstetrical care:
      (1) antenatal complications
      (2) delivery
      (3) postpartum care and education

III. MEDICAL SERVICES AVAILABLE ONLY IN ACUTE HOSPITAL

1. Surgery with major anesthesia (general or spinal).
2. Diagnostic tests, therapeutic procedures, and medications that are dangerous (or potentially dangerous), e.g., liver biopsy, cardiac catheterization, monitoring equipment, chemotherapeutic drugs, angiography.
3. Tests or procedures requiring scheduling too intense or complexity too great (e.g., equipment and/or personnel and/or expertise not available) for performance outside the acute hospital.
4. Patient's condition is too fragile to conduct tests as outpatient, because complications would be likely to occur, or the tests might be unsuccessfully performed.
5. Daily laboratory work on unstable conditions.
6. Traction for acute condition or acute exacerbation of chronic problem.
7. Radiation therapy for unstable patients.

IV. REHABILITATION SERVICES

1. Patient is undergoing intensive rehabilitation program requiring the involvement of various allied health professionals.
2. Intensive therapy or rehabilitation requires multiple sessions daily.
3. Initial rehabilitation efforts where there is rehabilitative potential and improvement is expected in a reasonable period of time.

V. PSYCHIATRIC SERVICES

1. Only when there is a concomitant acute medical condition.

VI. ADDITIONAL CONSIDERATIONS

1. The patient's condition requires more complete bedrest than available at home.
2. Condition is terminal, and it is appropriate to keep patient in the acute hospital for at most 14 days for humanitarian reasons.
3. The total number and intensity of skilled nursing services needed (to perform a combination of direct services, observations, and decision-making), are available in this hospital, but not in a Skilled Nursing Facility.
4. The patient is convalescing from an illness, and it is anticipated that his/her stay in a Skilled Nursing Facility would be less than 72 hours.

Figure 1.—The utilization review (UR) reviewer refers to these level-of-care guidelines while following the UR flowsheet (Figure 2). These guidelines provide representative examples of services available only in an acute-care hospital environment.

UCLA HOSPITALS AND CLINICS

LEVEL OF CARE: ADMISSION

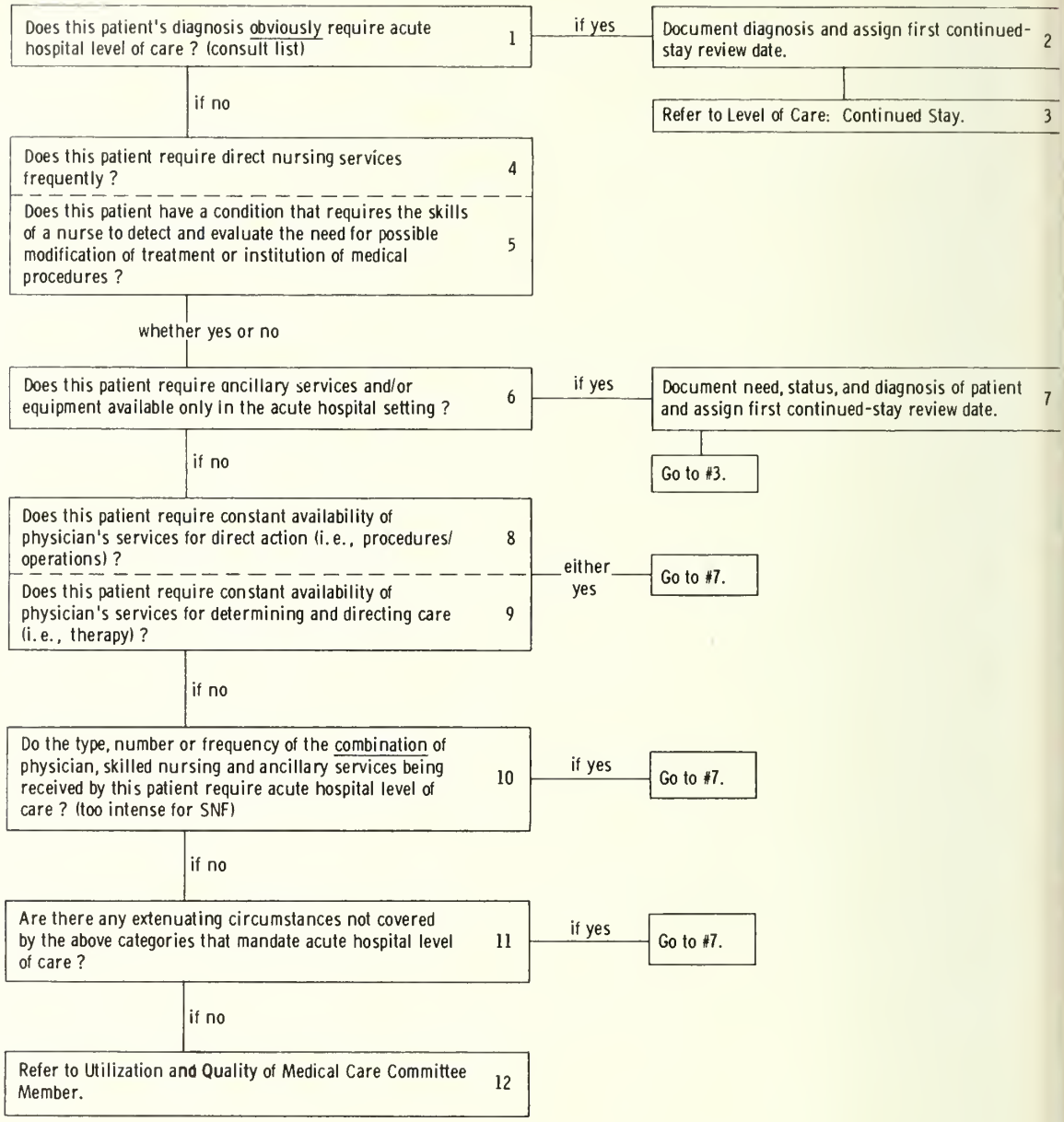
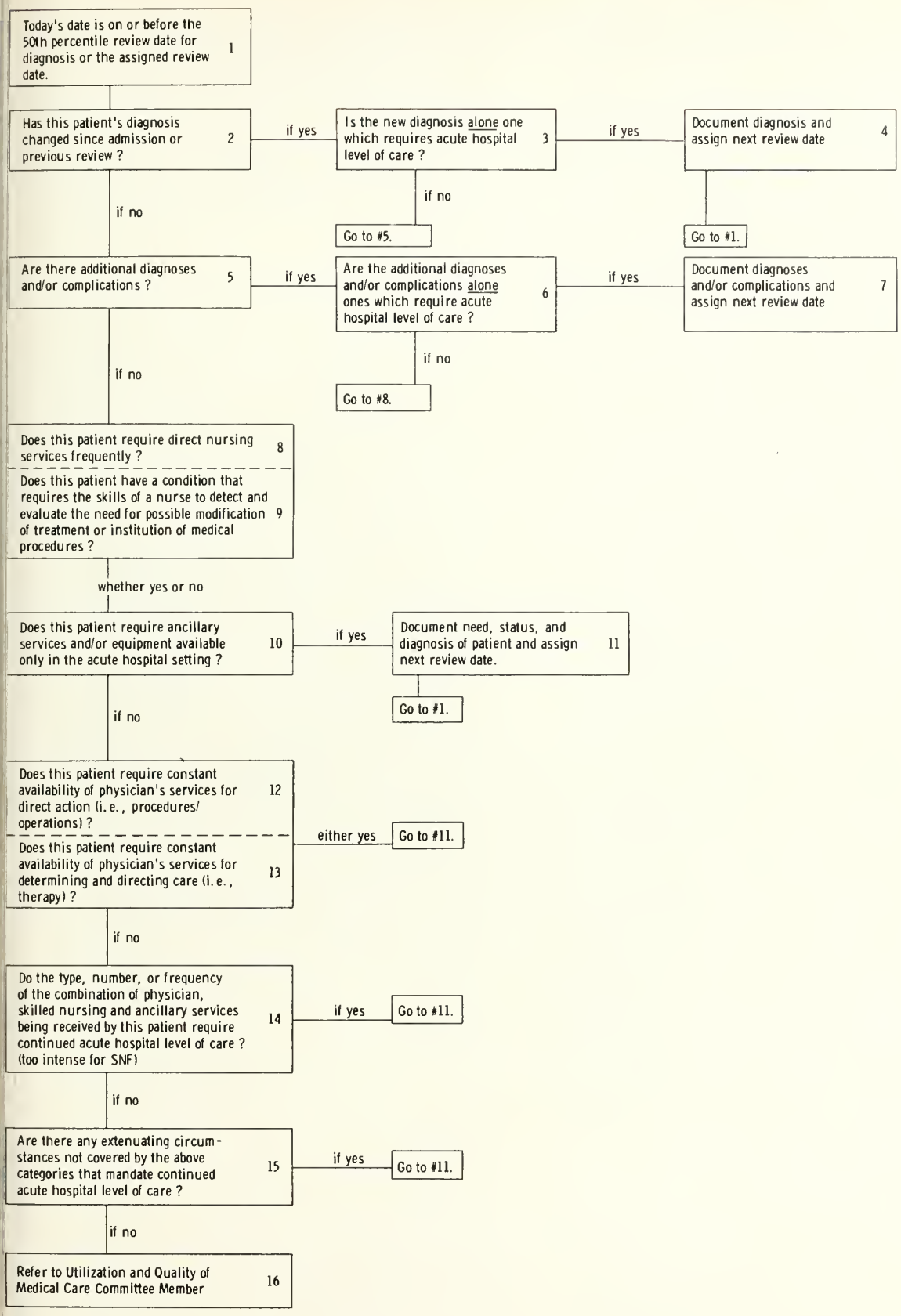


Figure 2.—The utilization review (UR) reviewer follows these flowshe (for upon-admission review and for continued-stay review) in order apply the level-of-care guidelines. Starting with box 1, and proceed in a direction dependent upon yes or no responses, the UR revie simultaneously documents the current level of care **and** reaches one two decisions: (1) assign next review date or (2) refer questionable c for further consideration and possible disapproval.


Today's date is on or before the 50th percentile review date for diagnosis or the assigned review date. 1
Has this patient's diagnosis changed since admission or previous review ? 2
if yes
Is the new diagnosis alone one which requires acute hospital level of care ? 3
if yes
Document diagnosis and assign next review date 4
if no
Go to #5.
Go to #1.
if no
Are there additional diagnoses and/or complications ? 5
if yes
Are the additional diagnoses and/or complications alone ones which require acute hospital level of care ? 6
if yes
Document diagnoses and/or complications and assign next review date 7
if no
Go to #8.
if no
Does this patient require direct nursing services frequently ? 8
Does this patient have a condition that requires the skills of a nurse to detect and evaluate the need for possible modification of treatment or institution of medical procedures ? 9
whether yes or no
Does this patient require ancillary services and/or equipment available only in the acute hospital setting ? 10
if yes
Document need, status, and diagnosis of patient and assign next review date. 11
Go to #1.
if no
Does this patient require constant availability of physician's services for direct action (i.e., procedures/ operations) ? 12
Does this patient require constant availability of physician's services for determining and directing care (i.e., therapy) ? 13
either yes
Go to #11.
if no
Do the type, number, or frequency of the combination of physician, skilled nursing and ancillary services being received by this patient require continued acute hospital level of care ? (too intense for SNF) 14
if yes
Go to #11.
if no
Are there any extenuating circumstances not covered by the above categories that mandate continued acute hospital level of care ? 15
if yes
Go to #11.
if no
Refer to Utilization and Quality of Medical Care Committee Member 16

UR physicians and UR coordinators in making rational, humane and explicable decisions concerning the appropriateness of location of patients in an acute-care hospital.

We believe that our level-of-care criteria can serve as an important, practical model for UR committees throughout the country. UR committees are likely to be attracted to level-of-care criteria, instead of to disease-specific criteria, because level-of-care criteria are inherently logical and are often advantageous for an acute-care hospital patient population. There are a number of specific advantages of level-of-care criteria over disease-specific criteria: (1) the application of disease-specific criteria is unsatisfactory for many patients who have multiple problems and diagnoses, since the disease-specific criteria are formulated for single diagnoses only; (2) level-of-care criteria can be effectively applied to indistinct cases where there exists no clear-cut diagnosis to which disease-specific criteria can be applied; (3) there is no need to develop a large number of disease-specific criteria for UR purposes, an advantage particularly important at a medical center such as UCLA, where there are so many different discharge diagnoses that every discharge diagnosis (with the single exception of that associated with delivery) accounts for fewer than 2 percent of all hospital discharges; (4) physician participation in the UR system is facilitated, because it is not necessary for a reviewing physician to have specific knowledge concerning diseases from specialty areas which are not his or her own, and (5) communication among UR coordinators, and between coordinators and physicians, is enhanced because there is a common basis to discuss the functioning of the review system, rather than multiple opinions concerning a specific disease process. None of these advantages is meant to imply that disease-specific criteria have no place in the review process; however, we believe that the UR function should make use nearly exclusively of level-of-care criteria. Disease-specific criteria remain necessary for review of quality of care (medical care evaluation studies), an area in which use of level of care criteria is inappropriate.

We cannot identify any major drawbacks to the level-of-care approach, so long as it is understood that level-of-care criteria are meant to be applied for purposes of review of (1) need for admission and (2) need for continued stay, and that they are not appropriate for review of quality of care. A barrier to the wider adoption of level-of-care criteria has been the unwillingness of a number of fledgling Professional Standards Review Organizations (PSRO's) to permit hospitals to make use of level-of-care criteria. We believe that such hesitancy is unwarranted, and is based on a misreading of the wishes of the federal government's guidelines, which have consistently reiterated that use of level-of-care criteria is acceptable.

Utilization Review Flowsheet

In order to assure the orderly application of these level-of-care guidelines, we borrowed the concept of "criteria mapping," that has been developed for purposes of quality-of-care review by Greenfield and co-workers,[6] and developed a flowsheet so that a UR reviewer, whether physician or UR coordinator, would be certain of asking all the right questions in the right order (see Figure 2).

The UR reviewer starts with the first question, and renders a judgment, based on the furnished guidelines. If the answer is yes, the reviewer proceeds to the next question (or required action) horizontally to the right. If the answer is no, the reviewer proceeds to the next question (or required action) vertically below. If there is only one action to follow, the reviewer automatically proceeds vertically below, to the next question (or action). This pattern persists until one of the two actions has taken place: the patient has been approved as requiring further acute-care hospital level of care (and, therefore, stay), or the patient's case must be presented to another reviewer because the initial reviewer has reached the conclusion (based on the guidelines) that an acute-care hospital level of care is not required. In either instance, medical judgment has been brought to bear in a channeled and guided manner.

The reader will note that we also developed a list of automatic diagnoses to justify admission to an acute-care hospital. We have not included a particular list, because most hospitals are well aware of this concept, and make use of such lists. It is useful to think of these conditions as conditions whose very presence implies a need for an acute-care hospital level of care, at least in the initial stages of treatment of the condition, whether new or a flare-up. At UCLA this group of conditions was purposely kept small. It will be enlarged only very slowly, as UR committee mem-

bers document to their satisfaction that there are additional conditions that, in actual practice at our particular hospital, always require an acute-care hospital level of care at the time of admission.

Also noteworthy is the fact that the level-of-care concept is relevant for both upon-admission review, and continued stay review. Separate, similar flowsheets were constructed for the two types of utilization review.

Utilization Review Function

Our level-of-care guidelines, list of automatic approval-upon-admission conditions and UR flowsheets for application of the guidelines have all been approved by the UCLA Hospital Utilization Review and Quality of Care Committee. They are being used routinely by our UR coordinators and by the UR physicians when our coordinators bring questionable cases to their attention. Therefore, our basis for judgment is explicit, and our criteria can be easily reviewed by outside inspecting agencies. Therefore, our decisions can be well-documented and well-defined when challenged either from within, or from outside our hospital.

We have also found these guidelines to be useful in orienting and training new UR coordinators and new physician members of the UR committee. The principles are easily grasped, and it is appreciated that the same principles can be applied no matter what the disease or problem and no matter if the question concerns the necessity for a new admission or the necessity for continued stay. Our coordinators and physicians view the level-of-care determination as being a logical way of deciding if the acute-care hospital environment is needed or not, and they do not find themselves deflected from an understanding of UR by personal reservations about particular items in a disease-specific group of criteria.

Similarly, the use of level-of-care criteria appears to have been a success vis-a-vis outside agencies. The local PSRO has accepted the UCLA level-of-care UR system as fulfilling its requirements, and considers level-of-care criteria to be the preferred method for carrying out the UR function. Third-party intermediaries, including Medi-Cal, have not increased their "questions" or "denials." And, although the application of these criteria would not necessarily be expected to have an effect (increase or decrease) on length of stay, it is gratifying to note that there has been no increase in length of stay.

It is obvious that no hospital can adopt, unchanged, the level-of-care criteria used by any other hospital. A hospital must adapt level-of-care criteria to its special internal and external circumstances. For example, level-of-care criteria will depend upon which services are offered and not offered by the particular hospital. Also, the level of care that can be provided only in an acute-care hospital depends upon what services are available in the less intensive facilities of the local community. To give an example, for a patient who requires rehabilitation and intravenously given medication, one community may have an unusual skilled nursing facility that can provide both, in which case the patient would not require the acute-care hospital level of care. Another community may have no skilled nursing facility capable of providing both; therefore, the same patient would indeed require an acute-care hospital level of care.

Although the level-of-care criteria will require adaptation, the flowsheet for applying the hospital's adapted level-of-care criteria can usually find use, unchanged.

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Refer to: Weinstein P, Gordon MJ, Gilson JS: A system for coding the presenting requests of ambulatory patients (Health Care Delivery). West J Med 126:324-329, Apr 1977

A System for Coding the Presenting Requests of Ambulatory Patients

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Effective methods developed to review and study the care of patients in hospital have not been applicable to ambulatory care, in which definitive diagnosis is the exception rather than the rule. A reasonable alternative to using diagnosis as the basis for assessing ambulatory care is to use the problems or requests presented by the patients themselves. A system has been developed for classifying and coding this information for flexible computer retrieval. Testing indicates that the system is simple in design, easily mastered by nonphysicians and provides reliable, useful data at a low cost.

METHODS FOR ASSESSING the quality of hospital care and the efficiency of providing it are used widely.[1-3] These methods are based on classification of patients into diagnostic groupings which permit the systematic collection, retrieval and subsequent analysis of health care problems. Data-processing techniques using computers can facilitate this process.

Review and study of the quality of ambulatory care is not well developed. Beyond general impressions, outpatient clinics are typically unable to characterize the type of patient "workload" that makes up their practice. Conventional diagnostic coding systems, such as the *International Classification of Disease, Adapted for Use in the United States* (ICDA)[4] and the *Standard Nomenclature*[5] serve well for patients in hospital but not for ambulatory patient populations, in which etiologic diagnoses are less frequently reached. At least two studies have reported that up to 25 percent of ambulatory patient problems never result in a final diagnosis.[6,7] Many of the problems are of an acute self-limited nature and have run their natural course before being identified. Also, chronic problems may persist for years without yielding a definitive diagnosis.

Patient Request Coding System

The delivery of ambulatory care begins with a patient's initial request for assistance and depends upon a series of decisions made by health care personnel who vary widely in training from receptionist to physician. Screening, treatment and re-

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ABBREVIATIONS USED IN TEXT

ICDA = International Classification of Disease, Adapted for Use in the United States

ICHPPC = International Classification of Health Problems in Primary Care

ferral frequently occur long before the point at which diagnosis is made. Storage and retrieval codes that depend on a diagnosis are therefore limited to retrieving those problems that have already passed through several critical phases of care and conform to recognized and well-defined syndromes. Such systems do not permit the identification and assessment of vague complaints, psychological difficulties and other requests brought to ambulatory care facilities by patients.

Assessing ambulatory outpatient care, therefore, requires a classification and retrieval system independent of diagnoses. Systems that classify physicians' impressions of patient problems have been found to be more useful in the review and study of ambulatory care.[8,9] The system described here permits the classification of problems at an even more elementary level, the request for help expressed by the patient himself before screening by medical personnel. Such a system, in conjunction with other types of codes, can permit the tracing of the entire ambulatory care sequence from initial requests for services to problem resolution. Adoption of such a system would result in two basis advantages: (1) neither diagnosis nor physician impressions would be a prerequisite for assessing ambulatory care and (2) there would be a focus on the patient's perception of the problem. A variety of studies may then investigate the delivery of ambulatory care at any point in the sequence. Moreover, the development of protocols or algorithms for the handling of given patient problems may be facilitated. The study of patient demands on ambulatory care settings has obvious and rich implications for assessment of community needs, administrative planning and staffing, patient education and curriculum planning in medical colleges. Further, the system may provide fertile ground for epidemiologic and health services research.

Review of Literature

Several systems have been developed for the coding of ambulatory patient problems. The authors reviewed the existing systems to determine whether they could be used to categorize effectively the full range of requests for service. To make this determination, a number of features were agreed upon as desirable attributes for the system:

- The system should allow for the classification of signs and symptoms *as presented by the patient*. The patient report orientation is without doubt the most fundamental departure from diagnosis-based codes. This attribute gives rise to several of the other requirements for a useful ambulatory care code.
- The system should have a coherent structure. Often the frequency of cases in a particular population is reported without attempting even rudimentary grouping or classification. Subclasses of problems, hierarchically nested, increase the usefulness of listings by presenting multiple levels of specificity useful in data retrieval, analysis and interpretation.
- The system should be both extensive and flexible. Patients present problems in a number of ways; we desire to retain whatever detail or lack of detail the patient may present. In order to maintain the fidelity of the patient's original statement, the code must allow for subjective patient perceptions, location by anatomical regions and descriptions of functional disorders.
- The system should permit use by nonphysicians. To permit this economy, the system should not require detailed knowledge of medical terminology or medical principles. The actual coding should be directed by a series of instructions or rules. Minimal judgment should be required of the coder. Health care workers with the skills of an experienced medical receptionist should be capable of providing low-cost, rapid, reliable coding.
- The system should permit use with minimal error. To assist a nonphysician user in locating the appropriate code and to assure that coding will be as accurate as possible, a simple set of instructions or rules for using the code should be available. The manual of rules and instructions should be cross-referenced in order to allow coders to quickly resolve discrepancies or ambiguities in the coding.
- The system should be amenable to low-cost data processing procedures. Coded problems should be capable of storage and retrieval using relatively simple programs. Costs should be within the range of private health care deliverers with small patient populations.

Review of the literature indicates that no one system has all of the aforementioned attributes.

Bain and Spaulding,[8] attempting to generate weighted differential diagnoses for common symptoms, developed an approach that permits patient-reported symptoms to be classified in a number of ways: anatomically, in a general symptomatic grouping, by system or function, or in a miscellaneous category. The system was, however, designed for use with a restricted population. Surgical, obstetric and dermatologic problems, and patients under the age of 14, are excluded.

Morrell, Gage and Robinson[9] developed a system to code symptoms presented by patients in general practice. Their approach was to define symptomatic groupings which include anatomical and functional subgroupings. Groupings for administrative requests and symptoms of early childhood are also included. There is, nevertheless, no general classification that could be used to code problems pointing only to anatomical location, such as "knee problems." Moreover, there is little room in the two digit code for the addition of new symptoms.

The International Classification of Disease, Adapted for Use in the United States (ICDA) has been modified for use in ambulatory care situations (H-ICDA) by the addition of common symptoms. However, this symptom code is not extensive, since it presupposes an attempt at diagnosis. It is expected that a number of coding ambiguities will result in a high likelihood of error. The recently published *International Classification of Health Problems in Primary Care* (ICHPPC) provides a much needed ambulatory companion to the ICDA. By leaving diagnosis at an appropriate level of generality and adding a supplementary classification for preventive, social and family problems, this system has achieved notable early success. Like the ICDA, however, it is intended to classify problems from the point of view of physicians.

Hurtado and Greenlick,[10] desiring to classify symptoms at a Kaiser-Permanente clinic, based their system on an organ system approach. Difficulty in coding diffuse and vaguely defined problems is also expected with this system. Renner[11] modified the Hurtado-Greenlick system by changing the code number assignments and the ordering of symptoms within categories. He also eliminated symptoms more appropriately classified as diagnoses, and added many new symptoms and other reasons for visits, as well as new modifiers. This sophisticated system met most of our requirements, but was judged to be too complex to be used accurately by minimally trained coders in diverse settings. High turnover typical of clerks and receptionists makes simplicity of classification an important concern.

All the systems reviewed are both coherent in structure and amenable to low-cost data processing procedures. However, no system includes all of the other four features. Several of the systems at present provide insufficient rules or instructions and are therefore subject to high rates of error. Other systems result in a large percent of problems being relegated to miscellaneous categories. With the exception of Renner's system, existing codes classify only diagnoses, symptoms and complaints, not the full range of patients' reasons for visits. In our experience these additional requests for service make up nearly 40 percent of the reasons for ambulatory visits.

The ICDA and the Hurtado-Greenlick systems, in addition to other difficulties, are based upon physician interpretation of symptomatology and are therefore inappropriate for our purposes. Morrell's system, though concerned with classification of patient-presented symptoms and amenable to nonphysician codification, is neither extensive nor flexible. The Bain-Spaulding symptom code, though excluding various patient populations, has three bases of symptom classification, allows for categorizing patient-presented problems by nonphysicians, and is flexible and adaptable to our purposes. The foundation of a complete, detailed patient request code was found in their system. Nonetheless, extensive revision was necessary to transform the Bain-Spaulding symptom code into a comprehensive classification system.

Development of the Patient Request Code

Patients presenting themselves for care within a three-week period in the summer of 1972 at Group Health Cooperative of Puget Sound's Family Health Center were used to develop a preliminary coding system. Duplicated copies of receptionists' appointment calendars resulted in a list of more than 3,500 patient requests which were then categorized. Nine independent categories of requests were developed.

Two feasibility studies were undertaken to determine: (1) if the patient request code could be used to gather statistical information about the demands on the health care delivery system and (2) if the patient request code could identify charts of patients with similar clinical characteris-

tics for purposes of audit, research, education or health care management. The code proved viable in both studies.

Useful practice profiles have been generated for individual physicians, specialty groups and whole clinics, spotlighting different patterns of demand for service. Other analyses have helped to isolate problems associated with inappropriate or disproportionate use of emergency services.

To date, the system has been used to audit three kinds of service requests: routine physical examinations, complaints of headache, and requests for a blood pressure check. Further audits are planned for conditions such as chest pain, fatigue and indigestion.

Subsequently, to facilitate systematic coding, an alphabetic index and a written set of rules for using the code were provided, along with a series of coding exercises to facilitate coder training. The entire set of materials was pilot tested on a sample of Group Health nurses, clinical assistants and receptionists.[12]

Results indicated that after an hour of training following normal working hours, a period of time in which superior performance was not expected, subjects learned to code at a rate of over 100 problems per hour, at 80 percent accuracy. Errors were generally trivial. Coders who worked rapidly were found to be more accurate in their coding. Moreover, receptionists did as well as clinical assistants and nurses, and were willing to code a reasonable number of hours in the future. Currently, the patient request code has been adopted by Group Health as an integral part of their automated medical record system. Moreover, the National Center for Health Statistics is considering several of the unique features of the classification system for inclusion into the planned revision of the National Ambulatory Medical Care Survey classification system.[13]

Organization of the Modified Code

On the basis of experience gained in the two feasibility studies and in the coder training tests, the original code was subsequently modified. The modified code consists of five independent categories. Patient requests may be coded under any or all of the categories. A tabular listing of patient requests and accompanying code numbers is shown in Figure 1. It should be noted that terms appearing in the listing are representative of many synonymous terms.

Category I: Symptom Code

The mainstay of the patient request code, the symptom code, is divided into three subcategories. Subcategories A (Anatomical Referent) and B (Lesion/Sensation Referent) may be employed either independently to code patient problems such as "stomach trouble" (41 99) or "cramps" (99 17), or together to code such problems as "stomach cramps" (41 17). Subcategory C (Functional/Systemic Referent) may be employed to code functional or systemic problems clearly referable to an organ system not found in Subcategories A or B, such as "indigestion" (0205).

Category II: Disease Name

At times patients present as their chief complaint a self-diagnosis or the diagnosis previously determined by their physician or others. Specific diseases are keyed to three-digit ICDA code numbers. Replacement of the ICDA by the ICHPPC is under consideration for entries in this category of the system.

*Category III: Therapeutic Procedures**

This category permits the coding of therapeutic procedures appropriate to the ambulatory care situation.

*Category IV: Preventive and Screening Diagnostic Procedures**

Used to classify physical examinations, laboratory and other diagnostic tests, and miscellaneous preventive measures, such as immunization and contraception.

Category V: Consultation and Counseling

This category includes requests for information, medical advice or therapeutic counseling.

Processing Procedures

The use of computers is almost essential for identifying patient cohorts and for manipulating data of interest to audit committees, researchers and administrators. The patient request classification system described here requires additional information such as a patient's age and sex, and the name of his usual physician, to aid retrieval,

*Where more detail is required, Categories III and IV may be replaced by existing codes such as *Current Procedural Terminology*.[14] We have found such codes to be too highly specific to be useful in this context. For example, patient requests such as "blood test" are uncodable using CPT.

Figure 1.—The Patient Request Code: A Tabular Listing of Patient Presenting Requests and Code Numbers

I. SYMPTOM CODE

The symptom code is composed of **either:**
- the 2 digit enatomic referent plus the 2 digit Lesion/Sensation referent

or
- the 4 digit Functional/Systemic referent

A. Anatomic Referent (to be used in conjunction with (B) Lesion/Sensation referent)

10 HEAD AND NECK
11 Eyes
12 Ears
13 Nose end sinuses
14 Mouth and tongue
15 Throat (including tonsils and "adenoid" glends)
16 Fece (including lips, cheeks, and forehead)
17 Jaw (including chin, gums, and dentition)
18 Neck
19 Other (head and neck)

20 CHEST
21 Breest
22 Nipple
23 Rib
24 Heart
25 Lung
29 Other (chest)

30 BACK
31 Lower back
32 Upper back
33 Spine
34 Disc
39 Other (back)

40 ABDOMEN
41 Stomach
42 Kidney, bladder, urinary tract
43 Liver
44 Gall bladder
45 Intestines
46 Appendix
47 Rectum, anus, colon, bowel (see Excretory, 0350)
48 Side, flenk
49 Other (abdomen)

50 UPPER EXTREMITIES
51 Shoulder
52 Arm
53 Underarm
54 Elbow
55 Wrist
56 Hand
57 Finger
59 Other (upper extremity)

60 EXTERNAL GENITALIA AND PELVIC AREA
61 Penis
62 Testes, scrotum
64 Uterus
65 Groin
66 Vagina
69 Other (genital)

70 LOWER EXTREMITIES
71 Hips
72 Buttocks
73 Thigh
74 Leg
75 Knee
76 Ankle
77 Foot
78 Toe
79 Other (lower extremity)

80 SKIN (not covered elsewhere)
81 Helr
82 Nall
83 Scalp
84 Other (skin)

MUSCULOSKELETAL (not covered elsewhere)
85 Muscle
86 Ligament end tendon
87 Joint
88 Bone
89 Other (musculoskeletal)

90 GLANDS
91 Prostate
92 Thyroid
93 Sweat
94 Lymph
98 Other (gland)

99 OTHER ANATOMICAL LOCATION OR REFERENCE TO LESION OR SENSATION AT UNNAMED LOCATION

B. Lesion/Sensation Referent

01 Pain, aching
02 Bleeding, discharge, not necessarily from wound or injury
03 Infection, inflammation, swelling
04 Discomfort, distress, tightness, squeezing, pressure
05 Congestion
06 Soreness, tenderness
07 Chenge in color (including pallor, jaundice, cyanosis, etc.)
08 Change in texture (including dryness, wrinkling, etc.)
09 Tumor, lump, mass
10 Tingling, burning, numbness, pins and needles
11 Weakness, paralysis
12 Limitation of movement, stiffness, difficulty
13 Deformity
14 Cramps, spasms; tics and tremors
15 Boil, pimple, sore
16 Rash, hives, spots
17 Growth, wart, mole, nodule, cyst, corn, callus
18 Itching and other skin irritations; insect bites
19 Obstruction

EXTERNALLY CAUSED TRAUMA
30 Injury, unspecified
31 Wound, stab, puncture, bite
32 Abrasion, scrape
33 Dislocation
34 Sprain, strain
35 Burn, blister (chemical, heat, or friction)
36 Foreign body
37 Bruise, contusion, concussion, bump
38 Fracture (actual or possible)
39 Other trauma
99 No lesion or sensation stated

C. Functional/Systemic Referent

0100 VISION
0101 Blurred vision
0102 Failing vision
0103 Double vision
0104 Spots in field of vision
0105 Shadows
0106 Blindness, one or both eyes
0107 Watery eyes
0108 Blood in eye
0109 Tearing
0149 Other (visual)

0150 AUDITORY
0151 Ringing, buzzing, roaring, etc. in ear or head; sensitivity to noises
0152 Diminished hearing
0153 Deafness, one or both ears
0154 Feeling of ears being blocked
0199 Other (auditory)

0200 DIGESTIVE
0201 Unusual taste
0202 Excess saliva
0203 Bad breath, odor
0204 Cracking or grinding of jaw
0205 Belching, bloating, gas, indigestion, heartburn
0206 Difficulty in swallowing
0207 Nausea
0208 Vomiting, regurgitating, retching
0209 Vomiting of blood
0249 Other (digestive)

0250 RESPIRATORY
0251 Cold, flu, upper respiratory infection
0252 Cough
0253 Coughing up blood
0254 Hoarseness, other voice changes
0255 Difficulty of breathing; shortness of breath; other breathing problems
0256 Snoring
0257 Sneezing, sniffling
0258 Wheezing, sighing respiration
0259 Sputum
0260 Hiccoughs
0299 Other (respiratory)

0300 CARDIOVASCULAR
0301 Palpitation and tachycardia
0302 Irregular heart beat
0303 High blood pressure (hypertension)
0304 Low blood pressure (hypotension)
0349 Other (cardiovascular)

0350 EXCRETORY, BOWEL MOVEMENTS
0351 Changed consistency of stool
0352 Changed color of stool
0353 Blood in stool
0354 Constipation
0355 Diarrhea
0356 Fecal incontinence for ages 5+
0369 Other (excretory)

0370 URINARY, BLADDER
0371 Painful or difficult urination; including burning
0372 Urinary frequency; excessive urination at night (nocturnal)
0373 Urinary urgency
0374 Urinary retention, urinary hesitency
0375 Diminished urine output
0376 Slowing of urinary stream
0377 Urinary incontinence for ages 5+
0378 Urinary bleeding
0379 Pus in urine
0380 Sugar in urine
0381 Unusual color of urine
0382 Unusual odor of urine
0399 Other (urinary)

0400 REPRODUCTIVE, INCLUDING GYNECOLOGIC
0401 Absence of menstruation
0402 Scanty menstruation
0403 Excessive menstruation
0404 Painful menstruation
0405 Frequent menstruation
0406 Irregular menstruation
0407 Intermenstrual bleeding
0408 Postmenopausal bleeding
0409 Menopause
0410 Other (menstrual)
0411 Dropping sensation
0412 Frigidity
0413 Painful coitus; painful erection
0414 Diminished or excessive libido
0415 Premature ejaculation
0416 Impotence
0417 Infertility, sterility
0418 Masturbation
0449 Other (reproductive)

0450 OBSTETRIC
0451 Suspected pregnancy
0452 Pregnancy
0453 Morning sickness
0454 Labor, labor pains
0455 Delivery
0456 Miscarriage
0457 Abortion
0458 Lactation, improper, painful, or problem with
0459 Other (obstetric)

0500 LOCOMOTOR
0501 Difficulty in walking; limping or lameness
0502 Disordered gait
0503 Inward toes
0504 Other (locomotor)

55 NEUROLOGIC

55 Dizziness, vertigo, balance
55 Disorder of speech, writing or reading
55 Disorder of memory, problem in concentration
55 Disturbance or loss of sensation
55 Convulsions, fits, seizures
55 Confusion, mental deterioration
55 Faintness, fainting, light-headedness, blackouts, loss of consciousness, coma, delirium
55 Other (neurologic)

60 PSYCHOLOGICAL—FOR AGES 5+

60 Depression, crying, unhappy, suicidal
60 Irritability
60 Hostile behavior; tantrum; destructiveness, negativism
60 Excessive use of stimulants or depressants, including alcohol
60 Fear, anxiety, worried, restless, tense, nervous, hysterical
60 Hallucinations, delusions
60 Marital problems
60 Personal problems
60 Nail biting
61 Smoking
61 Dreams, nightmares
64 Other (psychological)

65 FIRST FIVE YEARS OF LIFE

651 Irritability
652 Excessive dribbling
653 Hostile or aggressive behavior, tantrums, negativism
654 Refusing feedings; eating or feeding problem
655 Excessive crying; "colicky"
656 Diaper or other rash
657 Nursing (problem in)
658 Teething (problem in)
659 Weaning (problem in)
660 Toilet training, problem in; urinary or fecal incontinence
661 Fear of) Abnormal development—mental or physical
662 Sleep problem
663 Thumbsucking
664 Hyperactive
0665 Spitting up
0699 Other (age 0-5)

0700 GENERAL SYMPTOMS

0701 Ill, sick, rundown, malaise
0702 Weight excess, loss, or change; appetite, eating problems with ages 5+
0703 Fatigue, tiredness, energy problems
0704 Body temperature (Fever and/or chills)
0705 Fever blister
0706 Dehydration
0707 Hot flashes, sweating, feels hot
0708 Sleep problems, including insomnia
0709 Hyperactive
0710 Overdose
0711 Poisoning
0712 Reaction to medication
0713 Assault, non-sexual or unspecified
0714 Assault, sexual
0715 Accident
0716 Exposure to contagious disease
0717 Water retention; edema
0718 Excessive thirst
0749 Other (General symptoms)

II. REFERENT FOR DISEASE NAME OR SURGICAL PROCEDURE

Refer to 3 digit **ICDA** Code

III. REFERENT FOR NONSURGICAL, THERAPEUTIC PROCEDURES

01 Prescribe medication
02 Refill or check back on medications
03 Bandage, dressing, packing (apply, adjust, change, remove)
04 Suture
05 Cast, splint (apply, adjust, change, remove)
06 Remove warts or growth
07 Splinter removed
11 Lavage, irrigation, cleansing, washing
12 Catheterization, tube insertion
13 Cauterization
14 Enema
16 Injections, except immunizations
17 Kidney dialysis
18 Prosthetics, artificial body parts (fit, adjust, remove)
19 Appliances, e.g., crutches, neck brace (fit, adjust, remove)
20 Ultraviolet therapy
21 Grenz ray therapy, other x-ray therapy
22 Physical therapy and rehabilitation
23 Occupational therapy
24 Psychotherapy
25 Speech therapy
26 Vocational rehabilitation
99 Other (therapeutic procedures)

IV. REFERENT FOR SCREENING OR DIAGNOSTIC PROCEDURE

01 Adult physical examination at request of patient, doctor, or unspecified
02 Pelvic examination and/or Pap smear
03 Child physical examination (under 18 years, over one year)
04 Developmental physical examination (one year or less)
05 Premarital examination
06 Preadmission to hospital workup and post-hospital stay care
07 Postpartum examination
08 Sigmoidoscopy
09 Examination, other, at request of employer, school, camp, insurance, etc.
13 Sickle cell test
14 Tuberculosis test
15 Venereal disease test
16 Allergies test
17 Blood test
18 Blood pressure
19 Cholesterol test
20 Urine test
21 Throat culture
22 Culture, other
23 X-ray
24 Electrocardiogram
25 Pregnancy test
29 Immunizations
30 Contraceptives
99 Other (screening or diagnostic procedures)

V. REFERENT FOR CONSULTATION OR COUNSELING

1 Family planning/genetic counseling
2 Patient education
3 New patient
4 Expectant parent, child care, growth and development
5 Premarriage and sex counseling
6 Marital counseling
7 Diet counseling
8 Convalescent care
9 Other (counseling)

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description and cross-classification of patient charts. To increase the efficiency of data collection, personnel at the initial point of patient contact, usually the receptionist, may record the patient request and any additional information needed to complete the data set.

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Special Article

Refer to: Pheasant HC: Backache—Its nature, incidence and cost. West J Med 126:330-332, Apr 1977

Backache — Its Nature, Incidence and Cost

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In 1974 in California, 72,645 patients were admitted to hospital for backache. In 50 percent of these patients there was a diagnosis compatible with discogenic disease. Surgical treatment was done in 27 percent of the patients admitted to hospital. Total figures were determined for hospital costs and the costs of physician-related services. Costs for surgical treatment exceeded medical costs. Extrapolated to a national scale, it appears that the national cost for patients in hospital because of backache in 1974 was $1.38 billion. This does not include outpatient care expense or loss of income.

THE CALIFORNIA HEALTH DATA CORPORATION was founded in 1965 to act as an independent, regional health data organization. Its 1975 publication "Length of Stay in California Hospitals: 1974"[1] is a compilation of statistics derived from analysis of the discharge records of more than one million patients from 214 California hospitals. (This data base was a third of the total in California in 1974. The California experience is approximately 10 percent of the national experience.) These data include length of stay by diagnosis and length of stay by procedure (operation).

Nature and Incidence

In all, 13 diagnostic descriptors were selected (see Table 1). These should cover almost all conditions identified broadly as backache. Table 2 shows these procedural descriptors that identify operations. Both Table 1 and Table 2 include a column to indicate the total number of patients in each category, the average days' stay under these categories and a product of the number of patients multiplied by the average days' stay, in order to compute the total hospital/patient/bed/day figure for each diagnostic and procedural descriptor.

By subtracting the number of surgical (procedure) patients from the grand total (all descriptors) we identify those treated nonsurgically. This is important in computing costs, since both the hospital and physician charges are less for medically treated backache (Table 3).

From these tables, it can be seen that 45 percent of these patients discharged from hospital are identified as having discogenic disease (refer to Table 1 and note items 1 and 8). If incidence numbers for items 7 and 10 (radicular syndrome of lower extremities; sciatic neuritis) are added, the percentage of probable intervertebral disc disease becomes 50 percent. Fractures accounted for only 8.2 percent of the total.

In slightly greater than 27 percent of the patient total, surgical procedures were carried out.

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However, this group of patients used greater than 46 percent of the total hospital/patient/days.

Cost

Daily hospital charges are dependent upon total services provided. (Total services include but are not limited to the following items: drugs, both orally and parenterally given; radiological services; pathology and laboratory services; special care units; physical therapy; dressings; special trays for catheterization and the like, and special equipment, for example, air mattress or traction equipment.) This bears a direct relationship to the medical-surgical problem. The average hospital expense per day is less for a patient with a medically treated back problem than for one treated surgically. In 1974 this expense averaged approximately $140 a day for medical management, and $180 a day for surgically treated patients.[2] These costs are shown in Table 4. The discrepancy in cost between medical and surgically oriented modes of care is indicated by the percentage of total cost figures.

But these figures are only part of the total cost situation. Most patients with backache problems are treated as outpatients and will incur expense as well as loss of income. No statistical references could be found that identified outpatient cost for backache. Patients admitted to hospital also suffer loss of income. Since no method of evaluating loss of income or outpatient cost could be found, these elements of tangible cost are not included in these figures.

It is possible, however, to add recognized in-hospital physician services to this compiled information. To arrive at the figures listed in Table 5, certain assumptions have been made. A physician providing nonsurgical care would, upon admission of his patient to the hospital, carry out an initial examination (CRVS '74, Nos. 90200, 90215, or 90220)[3] and would follow

TABLE 1.—*Hospital Discharges Classified by Diagnosis*

	ICDA Diagnostic Code Number	*Descriptor*	*Number of Patients*	*Average Stay*	*Total Patient Days*
1	725.1	Prolapsed disc, lumbosacral	10,263	10.3	105,708.9
2	846.0	Sprain or strain, lumbosacral joint	4,665	7.4	34,521.0
3	728.7	Lumbalgia	2,164	7.3	15,797.2
4	805.2	Fracture and fracture-dislocation of vertebral column without mention of spinal cord lesion	1,925	9.8	18,865.0
5	847.8	Sprain or strain of other unspecified parts of back	1,813	7.4	13,416.2
6	728.9	Low back pain (not otherwise specified)	1,064	7.7	8,192.8
7	728.8	Radicular syndrome of lower extremities	770	8.3	6,391.0
8	725.9	Prolapsed disc at unspecified site	693	9.9	6,860.7
9	847.9	Sprain or strain, lumbar	459	7.0	3,213.0
10	373.0	Sciatic neuritis	399	7.8	3,112.2
11	717.0	Lumbago	None listed		
12	725.8	Prolapsed disc at specified site	None listed		
13	726.0	Disorder of sacroiliac joint	None listed		
		TOTAL (214 hospitals)	24,215	8.92	216,078.0
		CALIFORNIA TOTAL (X3)	72,645	8.92	648,234.0

ICDA = International Classification of Diseases Adapted

TABLE 2.—*Hospital Discharges Classified by Procedure (Operation)*

ICDA Procedural Code Number	*Procedure*	*Number of Patients*	*Average Stay*	*Total Patient Days*
83.4*	Excision, intervertebral cartilage (prolapsed disc)	4,455	14.2	63,261
03.0	Laminectomy	1,213	17.1	20,742
84.4†	Spinal fusion	1,013	15.8	16,005
	TOTAL (214 hospitals)	6,681	14.96	100,008
	CALIFORNIA TOTAL (X3)	20,043	14.96	300,024

*This is listed as 86.4 in Reference 1.
†This is listed as 87.4 in Reference 1.

TABLE 3.—*Surgical Versus Medical Management (Using Estimate of Total California Experience)*

	Number of Patients	*Percent*	*Total Patient Days*	*Percent*
All discharges	72,645	100.0	648,234	100.0
Surgical procedures	20,043	27.5	300,024	46.3
Medical treatment	52,602	72.5	348,210	53.7

TABLE 4.—*Hospital Cost*

	Number of Patient/ Bed/Days	*Cost*	*Total*	*Percent*
Medically treated	348,210	$140.00	$ 48,749,400	47.5
Surgically treated	300,024	180.00	54,004,320	52.5
			$102,753,720	

with daily visits (CRVS '74, Nos. 90240 or 90250).[3] We have estimated the initial charge to be $35 and the daily visits each $15 (the total hospital/bed/days were adjusted to reflect this assumption and difference).[4]

The consultant (surgeon) will normally charge a fee for consultation and a separate fee for any necessary subsequent surgical procedure. There is no way, at present, to determine consultation costs, and no estimate of this cost is included in these figures. We have included an average anaesthetic fee in determining the physician's portion of the surgically related medical costs. The average cost for anesthesia is estimated to have been $400[2] in 1974. A similar estimate of the average fee of a surgeon in 1974 was $900.[2] The assistant surgeon's fee of $180 represents 20 percent of the surgical fee. These additional costs are shown in Table 5.

The overall cost, both hospital and physician generated, for those Californians admitted to hospital for backache in 1974 is shown in Table 6. Surgically generated costs are now 60 percent of the total cost of backache. More important is the implication, through extrapolation, that our national cost in 1974 for hospital-treated back problems was probably about $1.38 billion. This amount represents 1.4 percent of all dollars expended for health care in the United States in 1974. (National total health care cost in 1974 was $104.03 billion.[5,p7])

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TABLE 5.—*Physician Costs (Charges)*

		(1) Initial Visit	*Daily Visit*	*Subtotal*	
Medical					
Number of patients	52,602	$ 35.00	$ ...	$ 1,841,070	
Hosptal/bed/days 348,210−52,602=296,608		...	15.00	4,449,120	
TOTAL					$ 6,290,190

		Anesthetic Fee	*Surgical Fee*	*Assistant Fee*	*Subtotal*	
Surgical						
Patients	20,043	$400.00	$ ...	$ ...	$ 8,017,200	
	20,043	...	900.00	...	18,038,700	
	20,043	...	...	180.00	3,607,740	
TOTAL						$29,663,640
TOTAL PHYSICIAN COST (in hospital)						$35,953,830

TABLE 6.—*Total Costs of Backache, California 1974*

	Hospital Cost (From Table 4)	*Physician Cost (From Table 5)*	*Subtotal*	*Percent*
Medical	$ 48,749,400.00	$ 6,290,190.00	$ 55,039,590.00	40
Surgical	54,004,320.00	29,663,640.00	$ 83,670,684.00	60
SUBTOTAL	$102,753,720.00	$35,953,380.00		
TOTAL			$138,707,550.00	

Refer to: Kagan BM: Ampicillin rash. West J Med 126:333-335, Apr 1977

Medical Information

Ampicillin Rash

BENJAMIN M. KAGAN, MD, *Los Angeles*

In some patients, a maculopapular rash occurs four or more days after the administration of ampicillin. It appears on the trunk and spreads peripherally, or it appears first on the extensor aspects of the limbs. It is not associated with urticaria and occurs more commonly in females than in males. It develops often in the presence of viral infection, infectious mononucleosis and certain other situations such as lymphatic leukemia, or in patients receiving allopurinol. This rash is not allergic in character. It does not become worse if treatment is continued and does not recur when ampicillin is given subsequently to the same patients. That there will be occasional, uncommon exceptions to this description must be accepted but in this, as in so many problems in medicine, physicians must be guided by the predominance of evidence.

This review was prompted by a request from the Advisory Panel on Pediatrics of the California Medical Association. The rash appearing during the administration of ampicillin occurs relatively frequently and is a source of concern especially if it establishes that a patient is allergic to a potentially lifesaving drug like penicillin. It is important therefore to review the evidence critically.

In a study by Bass and co-workers,[1] erythematous maculopapular skin rashes were observed in 3 percent to 7 percent of patients. There was some increase in incidence with increase in dosages but not to a significant degree. Urticarial skin rashes occurred in 1 percent of the patients and were unrelated to dose. This was a prospective study of 400 patients given four different dosage levels of ampicillin orally.

In another study[2] typical ampicillin skin rashes occurred in approximately 5 percent of 400 patients, an incidence comparable with that in other reports. Urticarial skin rashes which suggest true penicillin allergy occurred in less than 1 percent of all patients and were clearly not related to dose. This incidence of true penicillin allergy with ampicillin approximates that of other preparations of orally given penicillin.[3,4]

It is recognized that in patients with mononucleosis, an "ampicillin rash" is more likely to develop than in other patients. Nazareth and associates[5] reported their study involving 20 patients with infectious mononucleosis, all of whom had a typical rash when given ampicillin. After recovery from mononucleosis all were challenged with two doses of ampicillin given two weeks apart. In two of the patients a rash developed—an incidence of 10 percent. One of the two had a history of atopy and the other had previously reacted to penicillin. These results also suggest that the rash which developed due to ampicillin therapy was not in the nature of an allergic reaction that recurs and that therefore patients with an ampicillin rash may safely be given this drug again provided they have no history of atopy or penicillin sensitivity.

Kerns and co-workers[6] observed an incidence of 9.5 percent in 370 children. In none of the children with such a rash was there a positive skin test to penicillin or to penicillin major or minor determinants. Therapy with ampicillin was continued in 14 children with rash with no ill effects and with disappearance of the rash during therapy. Only one patient in the group in which rash developed and one in the group in which rash did not develop had serologic evidence of Epstein-Barr virus infection. These observations suggest that in many, an ampicillin rash occurs without infectious mononucleosis and also that patients with "ampicillin rash" are not at increased risk for a life threatening immediate or accelerated reaction to develop subsequent to future ampicillin or penicillin therapy.

Some authors have reported that a skin rash develops after the administration of ampicillin

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in the presence of infectious monoucleosis in more than 90 percent of the cases.[7-9] Bierman and associates[10] studied 40 cases of patients in whom a rash developed while ampicillin was being given. Of 30 patients with a maculopapular eruption, in none were there positive skin tests and in none were any other allergic manifestations noted. Of ten patients with urticaria, in three there were positive skin tests, and in five hemagglutinating antibodies were present. Five of these patients had other allergic phenomena.

In another study it was found that administration of allopurinol together with ampicillin also results in an increased incidence of rash.[11] In this study rashes occurred in about 7.5 percent of ampicillin recipients. However, the incidence in those who received ampicillin together with allopurinol was 22.4 percent.

Levantine reviewed the subject[12] and notes that many ampicillin rashes may not be due to true 6-aminopenicillanic acid nucleus hypersensitivity because benzyl and phenoxymethyl penicillins did not produce a high incidence of rash in infectious monoucleosis, yet this nucleus is common to all three drugs.

Nazareth[13] gave graduated doses of ampicillin to patients some months after ampicillin reactions had occurred but while they still had infectious mononucleosis. No rash or other hypersensitivity developed in any of the ten patients tested.

Cameron and Richmond[14] found a striking incidence of rash in patients with lymphatic leukemia treated with ampicillin (90 percent) and this observation together with the incidence in infectious mononucleosis suggests that abnormal antibodies and abnormal lymphocytes may have something to do with the reaction.

Also, against the allergic nature of the reaction are the facts that the incubation period is relatively short, anaphylaxis is infrequent, it has not been possible to show the presence of reagenic antibodies[15] and lymphocyte transformation tests are negative.[16]

The use of ampicillin in patients with infectious mononucleosis and also in those with cytomegalovirus mononucleosis should be avoided, its use in patients with lymphatic leukemia or reticulosarcoma should be restricted, and extra care should be used in prescribing it for patients with hyperurisemia and for patients receiving allopurinol.

Several studies suggest that the eruption is dose related.[17-19]

Harris and co-workers[20] point out that the rash most commonly appears on the extensor aspects of the limbs, especially the knees and ankles and that it is uncommonly associated with a general reaction. Most important, it rarely occurs less than four days after the start of ampicillin therapy.

Kroning and Denning[21] found the incidence of the rash in females in Germany was nearly three times that in males.

In a prospective study by a collaborative group of 933 patients[22] the overall incidence was 7.3 percent. The rash occurred most commonly in women and in patients suffering from viral infections. Of the 68 patients in whom a rash developed, in four there was slight swelling of peripheral joints and in two there were enlargements of superficial lymph nodes. In 12 of the 68, treatment was continued in spite of the rash, and in eight of these the rash was fading or disappeared by the end of treatment. Continuation of treatment was never followed by worsening of the rash or of symptoms. The authors conclude that the maculopapular rash which may develop about a week after starting treatment with ampicillin is unrelated to true penicillin allergy and may not even have an immunological basis.

On biopsy studies of the rash, perivascular and perifollicular aggregates of monouclear cells, principally lymphocytes in the dermis, are found. Skin irritation is present in two thirds of patients but is generally slight. Sometimes there is coalescence of lesions, purpura and slight fever.

Knudsen and co-workers[23] reported that purification of ampicillin with respect to protein impurities significantly reduces the incidence of rashes in treated paients. They suggest that one of the factors responsible for the rashes may be the presence of penicilloyl protein impurity in ampicillin.

Hendrikson[24] observed a higher incidence of rash when ordinary ampicillin was given than when a product free of "protein particles" was used.

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Techniques for Postcoital Tests

Evaluation of cervical factors for couples who are seen for the first time with infertility can be done by a screening six- or eight-hour postintercourse test. In the beginning, it is perhaps best to keep the postintercourse test at a low key since this is a rather stressful type of testing, especially to subject the husband to, on any sort of repetitive basis. If the couple has intercourse the night before and comes into the office the next morning, this usually provides an ample period of time to evaluate (in the average infertility problem) sperm migration within the cervical mucus. Naturally, the couple is instructed not to use any lubricants with intercourse. A speculum is put into the vagina and a specimen is taken from the endocervical canal, utilizing a 14- or 16-gauge medi-cut—that is, one in which the needle is thrown away and the plastic portion of the medi-cut is used to aspirate the specimen from the endocervical canal . . . . A coverslip is put over the first specimen and that is put aside for microscopic evaluation.

A second specimen is taken from the endocervical canal. A coverslip is dropped over it and then it is elevated to evaluate spinnbarkeit and the other physical properties of the cervical mucus. And in addition a pH study, utilizing simply litmus paper, is done with this mucous specimen. The second specimen is also saved if on the microscopic examination one identifies large amounts of bacteria or cellular debris that would suggest the need for a Gram stain. A third specimen is taken from the posterior fornix only if no sperm are identified in the endocervical specimens. If upon examination of the specimen from the endocervical canal, one sees 5 to 20 sperm per high-power field with good motion, then that is considered an adequate six- or eight-hour postcoital test. Naturally, there are couples in whom the six- or eight-hour postcoital test is not satisfactory. In that particular circumstance, one then reverts to the customary 2- or 2½-hour postcoital test. In other words, if the screening six- or eight-hour postcoital test is adequate, then one can discontinue further evaluation of cervical factors. However, if it is not normal, then to evaluate the cervical factors in that couple satisfactorally, it is necessary to assess the 2-hour or 2½-hour test.

—PAUL G. McDONOUGH, MD, *Augusta, GA*
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Medical Practice Questions

EDITOR'S NOTE: *From time to time medical practice questions of general interest are referred to the Scientific Board by the Peer Review Commission of the California Medical Association. Each is sent to members of the appropriate Scientific Advisory Panel.* Their responses are collated, reviewed and then submitted to the Peer Review Commission as the Scientific Board's opinion on the scientific and practice aspects of the question. The Commission adds suggestions to assist peer review units and authorizes publication.*

These opinions and positions are informational only and are not intended to be used as instructions, directives or policy statements. The appropriateness of care in individual cases should not be determined by these answers, but should be reviewed by local peer review committees.

Questions and reprint requests may be submitted to the Medical Practice Questions Committee, Peer Review Commission, California Medical Association, 731 Market Street, San Francisco, CA 94103.

Pulmonary Parasympathectomy

QUESTION:

Is pulmonary parasympathectomy considered accepted medical practice for the treatment of severe asthma? (Asked by Blue Shield of California)

OPINION:

In the opinion of the Advisory Panel on Chest Diseases, pulmonary parasympathectomy is not accepted medical practice for the treatment of severe asthma.

Panniculectomy with Intestinal Bypass

QUESTION:

(1) Should panniculectomy, when done during intestinal bypass surgical operation, be classified as a cosmetic or a reconstructive procedure? (2) Does panniculectomy reduce or increase the operative risk and incidence of postoperative complications of intestinal bypass surgical operation? (Asked by Blue Shield of California)

OPINION:

In the opinion of the Advisory Panel on General Surgery, panniculectomy is usually done as a separate procedure after an intestinal bypass operation has been carried out; however, there could be circumstances in which it would be reasonable to do this operation at the same time.

Most Advisory Panel members felt that panniculectomy is a reconstructive procedure. Opinion was evenly divided as to whether doing penniculectomy at the same time as intestinal bypass would increase the risk to the patient or whether this would depend on the circumstances of each individual case.

Cerebral Electrotherapy (CET)

QUESTION:

(1) Is cerebral electrotherapy (CET) acceptable medical practice for treating anxiety, body tension, insomnia, or psychosomatic disorders, or for use in opiate detoxification? (2) For any of the above for which cerebral electrotherapy is acceptable medical practice please list the recommended frequency and duration of treatment. (Asked by Blue Shield of California)

OPINION:

In the unanimous opinion of the Advisory Panels on Neurology, Physical Medicine and Rehabilitation and Psychiatry, cerebral electrotherapy (CET) is not a proven effective therapeutic modality for treating anxiety, body tension, insomnia or psychosomatic disorders, or for use in opiate detoxification. Cerebral electrotherapy should be considered experimental until controlled double-blind studies show it to have more than a placebo effect—such evaluative work is now in progress at the University of Texas and elsewhere. While the effectiveness of cerebral electrotherapy is questionable, it is a very safe procedure.

*The Scientific Board of the California Medical Association has a Scientific Advisory Panel for each of 23 recognized specialties of medical practice. Each Advisory Panel includes representation from the appropriate department of each of the eight medical schools in California, representatives of specialty societies in the field and representatives from the Specialty Sections of the Association. The Advisory Panels are thus broadly and authoritatively based in both academia and practice.

in memoriam

August, Charles Wilke, Kernville. Died February 4, 1977 in Kernville of heart disease, aged 51. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1954. Licensed in California in 1955. MD degree from California College of Medicine, 1962. Dr. August was a member of the Kern County Medical Society.

Berman, Jack Louis, Oakland. Died March 5, 1977 of heart disease, aged 54. Graduate of the University of Nebraska College of Medicine, Omaha, 1946. Licensed in California in 1949. Dr. Berman was a member of the Alameda-Contra Costa Medical Association.

Gourson, Nathaniel Edward, Burbank. Died February 13, 1977 in Burbank of cancer, aged 68. Graduate of the University of Vermont College of Medicine, Burlington, 1933. Licensed in California in 1938. Dr. Gourson was a member of the Los Angeles County Medical Association.

Gowdy, Ralph A., Los Angeles. Died January 13, 1977 in Los Angeles of heart disease, aged 90. Graduate of Chicago College of Medicine and Surgery, 1917. Licensed in California in 1927. Dr. Gowdy was a retired member of the Los Angeles County Medical Association.

Greco, Anthony J., Van Nuys. Died August 21, 1976, aged 80. Graduate of the University of Buffalo School of Medicine, 1917. Licensed in California in 1929. Dr. Greco was a retired member of the Los Angeles County Medical Association.

Groves, Robert Leroy, San Francisco. Died February 8, 1977 in San Francisco, aged 84. Graduate of the University of Illinois College of Medicine, Chicago, 1926. Licensed in California in 1926. Dr. Groves was a retired member of the San Francisco Medical Society.

Kleiman, Jerome, Huntington Beach. Died August 3, 1976 of cancer, aged 40. Graduate of Regia Università degli Studi di Bologna, Facoltà di Medicina e Chirurgia, 1964. Licensed in California in 1971. Dr. Kleiman was a member of the Orange County Medical Association.

Lake, Peter A., Palm Springs. Died August 2, 1976 of metastatic adenocarcinoma, aged 36. Graduate of the University of Miami School of Medicine, Coral Gables, 1964. Licensed in California in 1965. Dr. Lake was a member of the Riverside County Medical Association.

Markovitch, Marilyn, San Jose. Died February 20, 1977 in an automobile accident near Mariposa, aged 48. Graduate of Indiana University School of Medicine, Bloomington-Indianapolis, 1957. Licensed in California in 1966. Dr. Markovitch was a member of the Santa Clara County Medical Society.

McKinnon, Douglas David, Los Angeles. Died January 16, 1977 in Los Angeles, aged 77. Graduate of McGill University Faculty of Medicine, Montreal, 1927. Licensed in California in 1928. Dr. McKinnon was a member of the Los Angeles County Medical Association.

Nilsson, J. Paul, Corona. Died July 12, 1976 of myocardial infarction, aged 79. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1926. Licensed in California in 1926. Dr. Nilsson was a member of the Riverside County Medical Association.

Rousseau, Robert Earl, Santa Cruz. Died January 31, 1977 in Montana, aged 50. Graduate of Columbia University College of Physicians and Surgeons, New York, 1952. Licensed in California in 1957. Dr. Rousseau was a member of the Santa Cruz County Medical Society.

Scholz, Arnold M., Los Angeles. Died August 20, 1976 of a ruptured abdominal aneurysm, aged 85. Graduate of the College of Physicians and Surgeons, Medical Department, University of Southern California, 1914. Licensed in California in 1914. Dr. Scholz was a retired member of the Los Angeles County Medical Association.

Smith, James S., Los Angeles. Died August 5, 1976 of metastatic carcinoma, aged 73. Graduate of Howard University College of Medicine, Washington, DC, 1934. Licensed in California in 1965. Dr. Smith was a member of the Los Angeles County Medical Association.

Torru, Leonhard, San Francisco. Died February 10, 1977, aged 80. Graduate of Latvijas Universitate, Medicinas Fakultate, Riga, 1925. Licensed in California in 1952. Dr. Torru was a retired member of the San Francisco Medical Society.

Vieira, Frank Gonzolves, Stockton. Died February 8, 1977 in San Jose, aged 76. Graduate of the University of California Medical School, Berkeley-San Francisco, 1927. Licensed in California in 1927. Dr. Vieira was a retired member of the San Joaquin County Medical Society.

Wise, David C., Clayton. Died February 4, 1977 in Clayton, aged 82. Graduate of Washington University School of Medicine, St. Louis, 1921. Licensed in California in 1921. Dr. Wise was a retired member of the Alameda-Contra Costa Medical Association.

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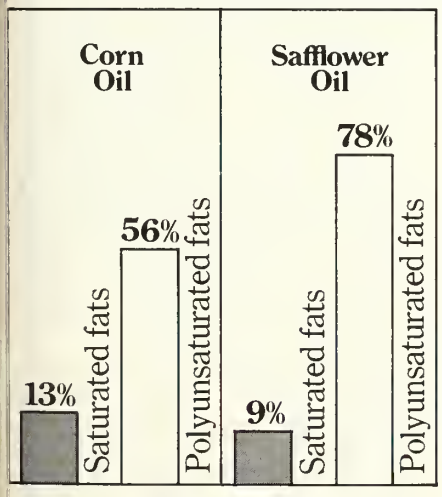

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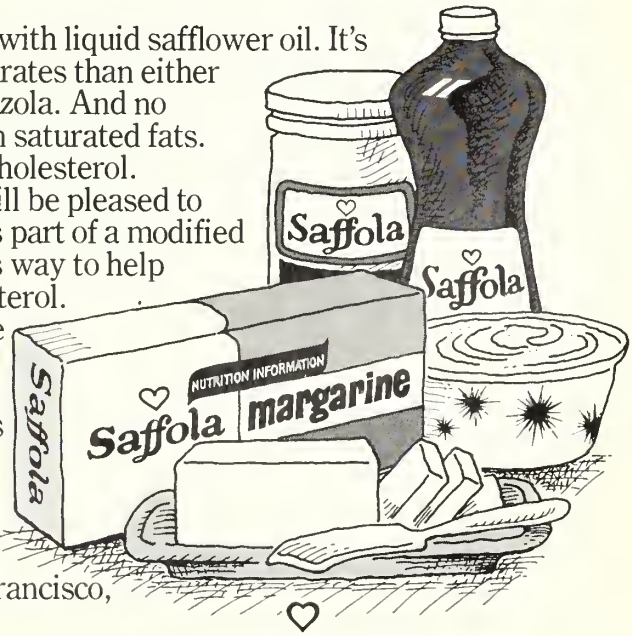

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(Continued from Page 18)

PHYSICIANS WANTED

OPEN-MINDED FAMILY PHYSICIANS (2) wanted by established family practitioner to share new office space in rural setting with room for plants and animals yet minutes to hospital and medical school. I am interested in feminism, homeopathy, profit sharing, medical teaching and alternative health care systems and a work schedule that allows personal growth and freedom. Contact Jacquelyn Wilson, MD, 14321 Penasquitos Dr., San Diego, Ca. 92129 (714) 487-5300.

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NATIONAL SPINAL CORD INJURY FELLOWSHIP—The California Regional Spinal Cord Injury Care System offers a HEW/Rehabilitation Services Administration funded Spinal Cord Injury Fellowship at Santa Clara Valley Medical Center to physicians, Board eligible or Board certified, in a medical or surgical related specialty, ie., Orthopedics, Urology, Internal Medicine, etc. The fellowship is one year in length and includes short rotating experiences in one or more other National Regional Spinal Cord Injury Centers, not to exceed four weeks. For further information contact: Glenn G. Reynolds, MD, Chairman, Physical Medicine and Rehabilitation, Santa Clara Valley Medical Center, 751 South Bascom Avenue, San Jose, California 95128.

CONFERENCES FOR MEDICAL PROFESSIONALS

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INTERNIST. Board certified. Wishes to relocate from a large city to a good family living area Western States. Reply Box 9517, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103

INTERNIST available for work in Bay Area. EKG reading and some teaching desirable. Reply to Box No. 9519, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

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PHYSICIAN AND SURGEON desires locum Tenant position in Office or emergency room for weekends, weeks or months. Available immediately. Licensed in California and Nevada. Please reply to P.O. Box No. 3725, San Clemente, California 92672.

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CANCER

April 22-23—**Medical and Surgical Treatment of Gastrointestinal Cancer.** Scripps Clinic Medical Institutions, La Jolla. Friday-Saturday. $50. Contact: Williamson B. Strum, MD, Scripps Clinic Med. Institutions, 10666 N. Torrey Pines Rd., La Jolla 92037.

May 14-15—**Skin Cancer.** UCSF. Saturday-Sunday.

May 21-22—**Management of Cancer—3rd Annual Workshop.** Institute for Cancer and Blood Research and Century City Hospital Radiation Therapy Center at Riviera Country Club, Pacific Palisades. Saturday-Sunday. 16 hrs. Contact: Howard R. Bierman, MD, Sci. Dir., Institute for Cancer and Blood Research, 140 N. Robertson Blvd., Beverly Hills 90211. (213) 655-4706.

June 20-24—**Head and Neck Oncology.** UCLA. Monday-Friday.

MEDICINE

April 16—**The Endocrine and Metabolic Aspects of Medical and Surgical Diseases—6th Annual Symposium.** South Coast Community Hospital, South Laguna. Saturday. 7 hrs. $40. Contact: Eugene B. Levin, MD, Dir. of Med. Ed., So. Coast Community Hosp., 31872 Coast Highway, So. Laguna 92677. (714) 499-1311.

April 16—**Gastroenterology.** Central San Joaquin Valley Area Health Education Center and Central Calif. Committee for Gastroenterology at Fresno Community Hospital, Fresno. Saturday. $35. Contact: Mr. Remi Barron, 5110 E. Clinton Way, Fresno 93728. (209) 252-2851.

April 18-22—**Advances in Internal Medicine.** UCSF. Monday-Friday.

April 23—**Controversies in Internal Medicine.** The San Jose Hospital and Health Center, Inc., and San Jose Hospital Foundation at Marriott's Great America, Santa Clara. Saturday. 6 hrs. $25. Contact: Stanley Skillicorn, MD, Dir. of Med. Ed., The San Jose Hosp. and Health Ctr., Inc., 675 E. Santa Clara, San Jose 95112. (408) 998-3212.

April 28-30—**New Approaches to Cardiac Diagnosis.** PMC at Fairmont Hotel, San Francisco. Thursday-Saturday.

May 6-7—**Update of Immunology and Allergy.** UCSD at Hilton Hotel, San Diego. Friday-Saturday.

May 7-14—**Diagnostic and Therapeutic Skills in Internal Medicine.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 30 hrs.

May 15-18—**American Thoracic Society—Annual Scientific Meeting.** Hilton Hotel, San Francisco. Sunday-Wednesday. Contact: Mr. S. R. Iannotta, Assoc. Ex. Dir., ATS, 1740 Broadway, New York 10019. (212) 245-8000.

May 18—**Atherosclerosis and Diet: A Practical Pediatric Approach.** American Heart Assn., Greater Los Angeles Affiliate; L.A. Pediatric Society at Bonaventure Hotel, Los Angeles. Wednesday. 6 hrs. Contact: Nancy Brown, AHA, Greater L.A. Affiliate, 2405 W. 8th St., Los Angeles 90057. (213) 385-4231.

May 20—**American Heart Association, California Affiliate—Scientific Sessions for Physicians.** Hyatt House, San Jose. Friday. Contact: Marilyn Probst, Admin. Asst., AHA, Calif. Affiliate, 1370 Mission St., San Francisco. (415) 626-0123.

May 20—**Stomatology.** STAN. Friday. 6 hrs.

May 20-21—**Hematology.** UCSF. Friday-Saturday.

May 21—**EKG Workshop.** PMC at Miyako Hotel, San Francisco. Saturday.

May 27-29—**New Concepts in Clinical Electrocardiography.** American College of Cardiology at Century Plaza Hotel, Los Angeles. Friday-Sunday. Contact: Mary Anne McInerny, Dir., Dept. of Cont. Ed. Prog., ACC, 9650 Rockville Pike, Bethesda, MD 20014.

June 1-July 27—**Review of ACP Medical Knowledge Self Assessment Test IV.** PMC. Wednesdays, 7-10 p.m.

June 4—**Pulmonary Artery Catheters and Ventilators.** PMC. Saturday.

June 6-October 18—**Intensive Review of Recent Advances in Internal Medicine—3rd Annual.** UCLA. Monday evenings.

June 7-10—**Echocardiography—Fundamentals and New Developments in Cardiac Ultrasound.** American College of

KEY TO ABBREVIATIONS AND SYMBOLS

Medical Centers and CMA Contacts for Information

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103. (415) 777-2000.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Duane Dillman, PhD, Director, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 564-5911, ext. 391.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr., MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, Ext. 2400.

PMC: Pacific Medical Center
Contact: Allen J. Enelow, MD, Chairman, Education Committee, Pacific Medical Center, P.O. Box 7999, San Francisco 94120. (415) 563-4321.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Neil C. Andrews, MD, Chairman, Department of Postgraduate Medicine, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, California College of Medicine, Irvine
Contact: Robert Combs, MD, Associate Dean, Continuing Medical Education, University of California, Irvine—California College of Medicine, Irvine 92717 (714) 833-5991.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, P.O. Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: David Allan, MD, Associate Dean for Continuing Medical Education, 1309 Basic Sciences Building, University of California, San Diego, School of Medicine, La Jolla 92037. (714) 452-3708.

UCSF: University of California, San Francisco
Contact: Malcolm S. M. Watts, MD, Associate Dean and Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 226-2047.

Cardiology at Town and Country Hotel, San Diego. Tuesday-Friday. Contact: Mary Anne McInerny, Dir., Dept. of Cont. Ed. Prog., ACC, 9650 Rockville Pike, Bethesda, MD 20014.

June 9-11—**Concepts and Controversies in Cardiology—1977.** Hospital of the Good Samaritan and American Heart Assn. of Greater L.A. at Hospital of the Good Samaritan, Los Angeles. Thursday-Saturday. Contact: Janie Sternal, Coord., CME, Hosp. of the Good Samaritan, 616 S. Witmer, Los Angeles 90017. (213) 488-8123.

June 18—**Allergy for the Office Practice.** PMC. Saturday.

June 24-26—**Dermatomycology.** UCSF. Friday-Sunday.

July 1-3—**Arthritis Education Workshop.** STAN. Friday-Sunday.

OBSTETRICS AND GYNECOLOGY

May 14—**Alternative Approaches to Childbirth.** UCLA. Saturday.

August 6-8—**Comprehensive Laparoscopy.** UCSD at Sea Lodge, San Diego. Saturday-Monday.

PEDIATRICS

April 15-16—**Aches, Pain and Dramatic Diseases in Children and Young Adults.** USC at Children's Hospital, Los Angeles. Friday-Saturday.

May 2-6—**Pediatric Review.** USC. Monday-Friday.

May 5-7—**Care of the Sick Newborn.** Memorial Hospital Medical Center, Long Beach. Thursday-Saturday. Contact: Houchang D. Modanlou, MD, 2801 Atlantic Ave., Long Beach 90801.

May 12-14—**Advances in Pediatrics.** UCSF. Thursday-Saturday.

May 16-18—**Psychological Aspects of Juvenile Diabetes.** See Psychiatry, May 16-18.

May 18—**Atherosclerosis and Diet: A Practical Pediatric Approach.** See Medicine, May 18.

May 30-June 1—**General Pediatrics—Annual Spring Meeting.** American Academy of Pediatrics, Northern Calif. Chapter 1, at Hyatt House, Monterey. Monday-Wednesday. 9 hrs. $100. Contact: Mrs. Helen Olson, Asst. Sec., AAP, No. Calif. Chapter 1, 2709 Calhoun St., Alameda 94501. (415) 522-8934.

June 17—**Conference on Prematurity—16th Annual.** STAN. Friday. Contact: Philip Sunshine, MD, Dept. of Pediatrics, Stanford Univ. Sch. of Med., Stanford 94305.

June 22-24—**Pediatric G.I. Course.** UCSF. Wednesday-Friday.

PSYCHIATRY

May 15-18—**New Therapeutic Approaches with Biofeedback.** UCLA at Biltmore Hotel, Santa Barbara. Sunday-Wednesday.

May 16-18—**Psychological Aspects of Juvenile Diabetes.** Diabetic Youth Foundation and American Diabetes Assn. at Bear Skin Meadow Camp. Monday-Wednesday. Contact: Diabetic Youth Foundation, 1128 Irvin St., San Francisco 94122. (415) 731-5113.

May 19-22—**Clinical Hypnosis—Introductory and Advanced Course.** See Of Interest To All, May 19-22.

June 3-4—**Psychosocial Care of the Dying Patient.** UCSF. Friday-Saturday.

June 26-July 1—**Comparative Psychotherapies.** USC at Vacation Village, San Diego. One week.

RADIOLOGY AND PATHOLOGY

April 29-30—**Sierra Valley Nuclear Medicine Association—Annual Symposium.** Sahara Tahoe Hotel, South Lake Tahoe. Friday-Saturday. Contact: Martha Frazer, Mercy San Juan Hospital, Dept. of Nuclear Medicine, 6501 Coyle Ave., Carmichael 95608.

May 14—**Radiological Evaluation of the Liver, Pancreas and Biliary Tract.** UCD at Woodlake Inn, Sacramento. Saturday.

June 3-5—**Spring Diagnostic Ultrasound Conference—2nd Annual.** Los Angeles Radiological Society at Century Plaza Hotel, Los Angeles. Friday-Sunday. Contact: Earl P. Detrick, MD, Westlake Community Hospital, 4415 Lakeview Canyon Rd., Westlake Village 91361.

June 18-25—**Lab Management for Pathologists.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week.

June 19-24—**Pathology of the Lung.** UCSD. Sunday-Friday.

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SURGERY AND ANESTHESIOLOGY

April 15-16—**Hand Injuries and Infections.** PMC. Friday-Saturday.

April 16—**The Endocrine and Metabolic Aspects of Medical and Surgical Diseases.** See Medicine, April 16.

April 21-22—**Diagnosis and Clinical Management of Glaucoma.** Jules Stein Eye Institute at Century Plaza Hotel, Los Angeles. Thursday-Friday. Contact: Jules Stein Eye Institute, UCLA School of Medicine, Los Angeles 90024.

April 21-22—**Phaco-Fragmentation.** UCSF. Thursday-Friday.

April 21-23—**General Surgery—Annual Course.** Thursday-Saturday.

April 23—**Audiology for Practicing Physicians.** PMC. Saturday.

April 28-29—**Current Problems in Intensive Care: Mechanical Ventilation.** UCSF at Stanford Court Hotel, San Francisco. Thursday-Friday. $125.

April 28-30—**Retina Workshop.** Retina Research Fund of St. Mary's Hospital and Medical Center, San Francisco, at Silverado, Napa Valley. Thursday-Saturday. 12 hrs. $135. Contact: Ms. Claire Ohiyon, c/o Howard Schatz, MD, 3637 Sacramento St., San Francisco 94118. (415) 921-4860.

April 30—**Flexible Bronchofibroscopy.** PMC. Saturday.

April 30-May 7—**Management of the Surgical Patient.** STAN at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week $275.

May 1—**Clarence E. Stafford Memorial Surgical Symposium and Lecture—2nd Annual.** White Memorial Medical Center, Dept. of General Surgery; and LLU at Hilton Hotel, Los Angeles. Sunday. 8 hrs. $40. Contact: Dept. of Gen. Surgery, White Mem. Med. Ctr., 1720 Brooklyn Ave., Los Angeles 90033. (213) 263-6100 or (213) 269-9131, ext. 429.

May 15-19—**Fifteenth Biennial Western Conference on Anesthesiology.** Hyatt Regency Hotel, San Francisco. Sunday-Thursday. 18 hrs. $100. Contact: Exec. Sec., BWCA, 707-2525 Willow St., Vancouver, B.C., Canada V5Z 3N8.

May 19-20—**Phaco-Fragmentation.** UCSF. Thursday-Friday.

May 19-21—**Neurosurgery—7th Annual Course.** UCSF at Hyatt on Union Square, San Francisco. Thursday-Saturday.

May 20-21—**Anesthesiology Refresher Course.** Biennial Western Conference on Anesthesiology at Del Monte Hyatt House, Monterey. Friday-Saturday. 8¼ hrs. $50. Contact: Exec. Sec., BWCA, 707-2525 Willow St., Vancouver, B.C., Canada V5Z 3N8.

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May 26-28—**Retina Workshop.** Retina Research Fund of St. Mary's Hospital and Medical Center, San Francisco, at Quail Lodge, Carmel Valley. Thursday-Saturday. 12 hrs. $135. Contact: Ms. Claire Ohiyon, c/o Howard Schatz, MD, 3637 Sacramento St., San Francisco 94118. (415) 921-4860.

June 3-4—**Ophthalmology Update II.** PMC. Friday-Saturday.

June 9-10—**Trauma.** UCSF at Mary's Help Hospital, Daly City. Thursday-Friday.

June 9-11—**Surgical Nutrition.** UCSF at Hilton Hotel, San Francisco. Thursday-Saturday.

June 9-12—**California Society of Anesthesiologists—Annual Scientific Meeting.** Town and Country Hotel, San Diego. Thursday-Sunday. Contact: CSA, 100 S. Ellsworth Ave., Suite 806, San Mateo 94401.

June 10-12—**Modern Laryngoscopy and Bronchoesophagoscopy: A Theoretical and Practical Course.** UCLA. Friday-Sunday. Contact: Paul H. Ward, MD, Div. of Head and Neck Surgery, UCLA Sch. of Med., Los Angeles 90024.

June 16-18—**Highlights of Ophthalmology.** PMC. Thursday-Saturday.

June 18-19—**American Association for Study of Headache.** See Of Interest To All, June 18-19.

July 2-9—**Manipulation, Mobilization and Related Techniques in Treatment of Musculo-Skeletal and Myofascial Pain Syndromes.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. $275.

August 6—**Intensive Care—Fifth Saturday Symposium.** See Of Interest To All, August 6.

August 6-13—**Ophthalmology.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week.

August 13-14—**Clinical Relevance of Recent Advances in Anesthesia: The Critically Ill Child and Adult.** STAN. Saturday-Sunday. 14 hours. Contact: Janie Sydow, Dept. of Anesthesiology, Stanford Univ. School of Medicine, Stanford 94305. (415) 497-6238.

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OF INTEREST TO ALL PHYSICIANS

April 15-16—**Aches, Pain and Dramatic Diseases in Children and Young Adults.** See Pediatrics, April 15-16.

April 15-16—**Practical ENT for Primary Physicians.** UCSF. Friday-Saturday.

April 16-23—**Emergency Medicine.** USC at Kona Surf Hotel, Kona, Hawaii. One week.

April 18-October 25—**Intensive Review of Family Practice.** USC. Thursday evenings.

April 20-June 29—**An Exploration of Traditional Chinese Health Care Practices.** UCLA. Wednesday evenings.

April 23—**Audiology for Practicing Physicians.** See Surgery, April 23.

April 28-29—**Current Problems in Intensive Care.** UCSF at Stanford Court, San Francisco. Thursday-Friday.

April 29—**Continuing Medical Education Seminar—6th Annual.** LLU at Bakersfield. Friday.

April 29-30—**San Joaquin Valley Counties Postgraduate Institute.** CMA at Ahwahnee Hotel, Yosemite. Friday-Saturday.

April 30—**Bedsores.** UCSD. Saturday.

May 6-8—**Family Medicine Intensive Review.** DREW. Friday-Sunday.

May 7—**8th Annual Symposium on Clinical Pharmacology.** STAN at Palo Alto Medical Clinic, Palo Alto. Saturday. Contact: Stanley Cohen, MD, Clinical Pharm., Dept. of Medicine, Stanford Univ. Sch. of Med., Stanford 94305. (415) 497-5315.

May 7-8—**Summer Emergencies.** Dept. of Emergency Medicine, Valley Medical Center, Fresno; San Joaquin Valley Area Health Education Center at Holiday Inn, Monterey. Saturday-Sunday. $80, physicians; $40, residents, students, nurses. Contact: Frank Mannix, MD, Dept. of Emergency Med., Valley Med. Ctr., 445 S. Cedar, Fresno 93702.

May 9-13—**Topics in Emergency Medicine.** UCSF at Franklin Hospital, San Francisco. Monday-Friday.

May 11-14—**California Blood Bank System—Annual Meeting.** Marriott Hotel, Los Angeles. Wednesday-Saturday. Contact: CBBS Central Office, P.O. Box 1340, Long Beach 90801.

May 16-20—**Postgraduate Institute for Emergency Physicians, Symposium I.** UCSD at Sheraton Harbor Island Hotel, San Diego. Monday-Friday.

May 16-22—**Diving Medicine.** UCSF at VA Hospital, Fresno. Monday-Sunday.

May 19-21—**Ambulatory Monitoring.** Medical Communications and Services Assn., STAN and Stanford Research Institute at Fairmont Hotel, San Francisco. Thursday-Saturday. 14 hrs. $100. Contact: Nancy Jacobsen, MCSA, 1107 N.E. 45th St., Rm. 315, Seattle, WA 98105. (206) 633-0505.

May 19-22—**Clinical Hypnosis—Introductory and Advanced Course.** American Society of Clinical Hypnosis at San Francisco. Thursday-Sunday. 25 hrs. $225. Contact: William F. Hoffman, Jr., Exec. Sec., ASCH, Education and Research Foundation, 2400 E Devon Ave., Suite 218, Des Plaines, ILL 60018. (312) 297-3317.

May 21-22—**Family Practice Management of Ischemic Heart Disease.** UCLA. Saturday-Sunday.

May 22-27—**Fingers-to-the-Toes—An Orthopedic Approach for the General Practitioner.** UCD at Stanford Sierra Camp, Fallen Leaf Lake. Sunday-Friday.

May 25-27—**Pain: Diagnosis and Management.** UCLA. Wednesday-Friday.

May 26-30—**Patient Oriented Applied Medical Advances.** UCSF at Hawaii. Thursday-Monday.

June 3-4—**Psychosocial Care of the Dying Patient.** See Psychiatry, June 3-4.

June 8-12—**California Chapter, American College of Emergency Physicians—Scientific Assembly.** Fairmont Hotel, San Francisco. Wednesday-Sunday. Contact: Calif. Chapter, ACEP, 58 California Ave., Orinda 94563.

June 9-11—**Management of Medical Problems.** PMC. Thursday-Saturday.

June 16-17—**Sports Medicine.** USC. Thursday-Friday.

June 18-19—**American Association for Study of Headache—Annual Meeting.** Hyatt on Union Square, San Francisco. Saturday-Sunday. Contact: Seymour Diamond, MD, Exec. Sec., Am. Assn. for Study of Headache, 5252 N. Western Ave., Chicago 60625. (312) 878-5558.

June 18-22—**American Medical Association—126th Annual Convention.** Fairmont Hotel, San Francisco. Saturday-Wednesday. Contact: AMA, 535 N. Dearborn St., Chicago 60610.

June 20-24—**Postgraduate Institute for Emergency Physicians, Symposium IV.** UCSD at Islandia Hotel, San Diego. Monday-Friday.

July 11-15—**Postgraduate Institute for Emergency Physicians, Symposium III.** UCSD at Hilton Hotel, San Diego. Monday-Friday.

July 31-August 5—**National Medical Association—82nd Annual Scientific Assembly.** Bonaventure Hotel, Los Angeles. Sunday-Friday. Contact: Alfred F. Fisher, Exec. Dir., NMA, 1625 Eye St., NW, Suite 725A, Washington, D.C. 20006.

August 6—**Intensive Care—Fifth Saturday Symposium.** Mercy Hospital and Medical Center, San Diego. Saturday. 8 hrs. Contact: Gilbert E. Kinyon, MD, Dir. of Anesthesia and Respiratory Therapy, Mercy Hosp. and Med. Ctr., 4077 Fifth Ave., San Diego 92103. (714) 294-8037.

August 13-24—**Postgraduate Refresher Course—20th Annual.** USC at Hawaii. 11 days. 37 hrs.

August 15-19—**Postgraduate Institute for Emergency Physicians, Symposium II.** UCSD at Islandia Hotel, San Diego. Sunday-Thursday.

August 22-27—**Family Practice Refresher Course—5th Annual.** UCD at Del Monte Hyatt House, Monterey. Monday-Saturday.

August 30-October 18—**Evening Lectures in Medicine.** UCSF at Oakland Hospital, Oakland. Tuesday evenings.

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PRECEPTORSHIPS AND TRAINEESHIPS

Training for Physicians in General Internal Medicine. LLU. Four weeks or more, by arrangement. Bedside and classroom training, practical aspects of clinical care and management. 160 hrs. Contact: John E. Peterson, MD, LLU.

Training of Physicians in Modern Concepts of Pulmonary Care. LLU. Four weeks or more, by arrangement. Diagnostic and therapeutic methods in medical chest disease, physiological methodology of modern pulmonary care programs, use of new instrumentation in the field. 160 hrs. Contact: John E. Hodgkin, MD, Chief, Section of Medical Chest Diseases, LLU.

Physician-in-Residence Preceptorship in Pulmonary Disease. USC, Pulmonary Disease Section, Dept. of Medicine and Postgraduate Medical Education. One month or more, by arrangement. Opportunity for practicing physician to achieve specified knowledge and skills in adult pulmonary medicine. Contact: Oscar J. Balchum, MD, PhD, USC.

Training for Physicians in Nephrology. LLU. Four weeks or more, by arrangement. Hemodialysis, peritoneal dialysis, renal biopsy, and kidney transplantation. 160 hrs. Contact: Robert E. Soderblom, MD, LLU.

Preceptorships in Cardiology. PMC. By arrangement. $200 per mo.; $500 for 3 mos. Contact: Arthur Selzer, MD, PMC.

Preceptorships in Practical Office Dermatology. PMC. Wednesdays or Fridays, 9:00 a.m.-12:00 noon, for 10 weeks. Periods begin Oct., Jan., or April. $100. Contact: Harold M. Schneidman, MD, Dept. of Dermatology, PMC.

Preceptorships in Infectious Disease. PMC. Full time for four weeks. To be arranged. $250. Contact: Rodney J. Valentine, MD, Chief, Div. of Infectious Diseases, PMC.

Preceptorships in Basic Sciences, Biochemistry and Biophysics, Dermatology, Echocardiography, International Health, Microbiology, Neurological Surgery, Obstetrics and Gynecology, Pediatrics, Pharmacology and Experimental Therapeutics, Physiology, Psychiatry, Urology. UCSF. By special arrangement.

Traineeships in Renal Dialysis. UCSF. By special arrangement.

OREGON

COUNCIL ON MEDICAL EDUCATION

THIS BULLETIN of information regarding continuing education programs and meetings of various medical organizations in Oregon is supplied by the Council on Medical Education of the Oregon Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Council on Medical Education, Oregon Medical Association, 5210 SW Corbett Ave., Portland, OR 97201; or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

University of Oregon Medical School, Department of Internal Medicine, 3181 SW Sam Jackson Park Road, Portland 97201:

Every Tuesday, 8:00 a.m. to 9:00 a.m.—**Internal Medicine Grand Rounds.** Library Auditorium, University of Oregon Health Sciences Center, Portland. Contact: Stephen R. Jones, MD, Department of Internal Medicine, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, 97201.

Providence Medical Center, 700 NE 47th Avenue, Portland 97213:

Every Wednesday, 8:00 a.m. in the auditorium—**Spring Medical Grand Rounds,** Providence Medical Center. Contact: David N. Gilbert, MD, Director of Medical Education, Providence Medical Center, 700 NE 47th, Portland 97213.

University of Oregon Medical School, Infectious Disease Conferences, 3181 SW Sam Jackson Park Road, Portland.

Every Thursday, 12:00 Noon—**Infectious Disease Conference** (through June 2), Room 8B-60 UHS (University Hospital South).

FAMILY PRACTICE

Every Wednesday, 11:00 a.m. to 12:00 Noon. **Family Practice Grand Rounds.** Family Practice Center, University of Oregon Health Sciences Center. Contact: William A. Fisher, MD, University of Oregon Health Sciences Center, Department of Family Practice, 3181 SW Sam Jackson Park Road, Portland 97201.

May 5-8—**Oregon Academy of Family Physicians 30th Annual Scientific Assembly.** Salishan Lodge, Gleneden Beach. Contact: Skippie Patterson, Executive Secretary, Oregon Academy of Family Physicians, 2188 SW Main, Portland 97205.

May 19—**Woodland Park Hospital Family Practice Symposium.** Main Auditorium, Woodland Park Hospital. Contact: Robert T. Childs, MD, 10300 NE Hancock Street, Portland 97220.

INTERNAL MEDICINE

Every Tuesday, 8:00 a.m. to 9:00 a.m.—**Internal Medicine Grand Rounds.** Library Auditorium, University of Oregon Health Sciences Center, Portland. Contact: Stephen Jones, MD, Department of Internal Medicine, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland 97201.

May 12-14—**Oregon Society of Internal Medicine and Oregon Chapter American College of Physicians Joint Annual Scientific Session.** Sunriver Lodge, Sunriver, Oregon. Contact: Donald R. Olson, MD, Oregon Society of Internal Medicine, 5210 SW Corbett Street, Portland 97201.

OF INTEREST TO ALL PHYSICIANS

April 19—**Emotional Aspects of Having a Heart Attack.** Rogue Valley Memorial Hospital Classroom Auditorium, Medford. Contact: Oregon Heart Association, 1500 SW 12th Avenue, Portland 97201.

April 20—**Biofeedback in Medicine.** Withycombe Hall, Oregon State University, Corvallis. Contact: R. L. Phillips, Ads A 600 Oregon State University, Corvallis 97331.

April 21-22—**Oregon Heart Association 1977 Scientific Session.** Sheraton Lloyd Center, Portland. Contact: Oregon Heart Association, 1500 SW 12th Avenue, Portland 97201.

May 20-22—**Sports Medicine Course.** Oregon State University, Corvallis. Contact: Dr. Steven Roy, Oregon State University, Student Health Center, Corvallis 97330.

WASHINGTON, ALASKA, MONTANA AND IDAHO

In order to have future activities listed here or to receive information on these and other activities, please write Ms. Joan M. Kelday, Information Specialist, Continuing Medical Education, WAMI Program, University of Washington School of Medicine, Health Sciences Building, SC-64, Seattle, Washington 98195. Phone: (206) 543-6995.

April 14-15—**Respiratory Care.** Thursday-Friday. Seattle. Contact: Pat Lind, Div. of CME, HSB SC-50, Univ. of Wash. Sch. of Med., Seattle, WA 98195. (206) 543-9495 or 543-1050.

April 14-17—**Society for Obstetric Anesthesias and Perinatology.** Thursday-Saturday. Edgewater Inn, Seattle. Contact: D. H. Ralston, MD, Department of Anesthesiology, RN-10, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-4172.

April 15-16—**Nutrition for Physicians.** Friday-Saturday. Seattle. Contact: Pat Lind, Div. of CME, HSB SC-50, Univ. of Wash. Sch. of Med., Seattle, WA 98195. (206) 543-9495 or 543-1050.

April 19—**Surgery: Cancer and Trauma of the Head and Neck.** Tuesday. Univ. of Wash. in Missoula, Mont. 7-9 p.m., Community Hospital. 2 hrs. Contact: Mrs. Janet Perrin, 500 West Pine, Missoula, MT 59801. (406) 549-3782.

April 20—**Surgery: Cancer and Trauma of the Head and Neck.** Wednesday. Univ. of Wash. in Billings, Mont. 1-3:30 p.m., Marillac Hall. 2½ hrs. Contact: Mrs. Frances Burt, Cont. Med. Ed. Marillac Hall, Billings, MT 59101. (406) 252-2121, Ext. 258.

April 22-23—**Cancer Symposium: Supportive Care of the Patient with Advanced Cancer.** Friday-Saturday. Glacier Auditorium, Swedish Hospital Medical Center, Seattle. $35. Hours to be determined. Contact: John L. Wright, MD, Dir. Med. Ed., Swedish Hospital Medical Center, 747 Summit, Seattle, WA. (206) 292-2265.

April 25—**Internal Medicine Review: Upper Intestinal Diseases —Esophagus to Ileum.** Monday. Univ. of Wash. in Wenatchee, Wash. 7-9 p.m., Wenatchee Valley Clinic. 2 hrs. Contact: William M. McKee, MD, P.O. Box 489, Wenatchee, WA 98801. (509) 663-8711.

April 26—**Internal Medicine Review: Upper Intestinal Diseases —Esophagus to Ileum.** Tuesday. Univ. of Wash. in Yakima, Wash. 5-7 p.m., Memorial Hosiptal. 2 hrs. Contact: Harry Kimball, MD, Yakima Medical Center, Yakima, WA 98902. (509) 248-6791.

April 28—**Internal Medicine Review: Upper Intestinal Diseases —Esophagus to Ileum.** Thursday. Univ. of Wash. in Billings, Mont. 7-9:30 a.m., Marillac Hall. 2½ hrs. Contact: Mrs. Frances Burt, Cont. Med. Ed., Marillac Hall, Billings, MT 59101. (406) 252-2121, Ext. 258.

April 29—**Internal Medicine Review: Upper Intestinal Diseases —Esophagus to Ileum.** Friday. Univ. of Wash. in Missoula, Mont. 8:30-11 a.m., St. Patrick Hospital. 2 hrs. Contact: James E. Gouaux, MD, 515 Kensington, Missoula, MT 59801. (406) 549-4581.

April 29-30—**Medical Alcoholism.** Friday-Saturday. Seattle. Contact: Pat Lind, Div. of CME, HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle, WA 98195. (206) 543-9495.

May 6-7—**Dermatology.** Friday-Saturday. Seattle. Contact: Pat Lind, Div. of CME, HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle, WA 98195. (206) 543-9495.

May 7-8—**West Coast Anesthesiology Residents' Conference.** Saturday-Sunday. Virginia Mason Medical Center Auditorium, Seattle. Hours and fee to be determined. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) 223-6898.

May 6-7—**High-risk Mother and Infant.** Friday-Saturday. Seattle. Contact: Pat Lind, Div. of CME, HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle, WA 98195. (206) 543-9495.

May 13-14—**Perioperative Care of the Surgical Patient.** Friday-Saturday. Virginia Mason Medical Center Auditorium, Seattle. 9 hrs. $75. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) 223-6898.

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May 18—**Evaluation of Acute Trauma.** Wednesday. Univ. of Wash. in Anacortes, Wash. 7:30-10 a.m., Island Hospital. 2½ hrs. Contact: Harry Eiesland, MD, 24th and M Ave., Anacortes, WA 98221. (206) 292-3101.

May 19-20—**Fluid Electrolyte Disorders: A Clinical Approach.** Thursday-Friday. Virginia Mason Medical Center Auditorium, Seattle. Hours and fee to be determined. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) 223-6898.

May 20-21—**Coronary Bypass Surgery.** Friday-Saturday. Seattle. Contact: Pat Lind, Div. of CME, HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle, WA 98195. (206) 543-9495.

May 23—**Internal Medicine Review: Medical Genetics.** Monday. Univ. of Wash. in Wenatchee, Wash. 7-9 p.m., Wenatchee Valley Clinic. 2 hrs. Contact: William M. McKee, MD, PO Box 489, Wenatchee, WA 98801. (509) 663-8711.

May 24—**Internal Medicine Review: Medical Genetics.** Tuesday. Univ. of Wash. in Yakima, Wash. 5-7 p.m., Memorial Hospital. 2 hrs. Contact: Harry Kimball, MD, Yakima Medical Center, Yakima, WA 98902. (509) 248-6791.

May 26—**Internal Medicine Review: Radiologic Aspects of Internal Disease.** Thursday. Univ. of Wash. in Billings, Mont. 7-9:30 a.m., Marillac Hall. 2½ hrs. Contact: Mrs. Frances Burt, Cont. Med. Ed., Marillac Hall, Billings, MT 59101. (406) 252-2121, Ext. 258.

May 27—**Internal Medicine Review: Radiologic Aspects of Internal Disease.** Friday. Univ. of Wash. in Missoula, Mont. 8:30-11 a.m., St. Patrick Hospital. 2½ hrs. Contact: James E. Gouaux, MD, 515 Kensington, Missoula, MT 59801. (406) 549-4581.

June 3-4—**Ophthalmology for the Non-Ophthalmologist.** Friday-Saturday. Virginia Mason Medical Center Auditorium, Seattle. Hours and fee to be determined. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) 223-6898.

June 17-18—**Mountaineering Medicine.** Friday-Saturday. Virginia Mason Medical Center Auditorium, Seattle. Hours and fee to be determined. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) 223-6898.

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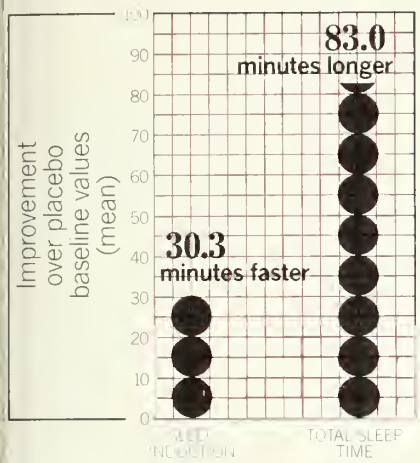

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Indications: Effective in all types of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings and/or early morning awakening; in patients with recurring insomnia or poor sleeping habits; in acute or chronic medical situations requiring restful sleep. Since insomnia is often transient and intermittent, prolonged administration is generally not necessary or recommended.
Contraindications: Known hypersensitivity to flurazepam HCl.
Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. Caution against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving).
***Usage in Pregnancy:* Several studies of minor tranquilizers (chlordiazepoxide, diazepam, and meprobamate) suggest increased risk of congenital malformations during the first trimester of pregnancy. Dalmane, a benzodiazepine, has not been studied adequately to determine whether it may be associated with such an increased risk. Because use of these drugs is rarely a matter of urgency, their use during this period should almost always be avoided. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**
Not recommended for use in persons under 15 years of age. Though physical and psychological dependence have not been reported on recommended doses, use caution in administering to addiction-prone individuals or those who might increase dosage.
Precautions: In elderly and debilitated, limit initial dosage to 15 mg to preclude oversedation, dizziness and/or ataxia. Consider potential additive effects with other hypnotics or CNS depressants. Employ usual precautions in patients who are severely depressed, or with latent depression or suicidal tendencies. Periodic blood counts and liver and kidney function tests are advised during repeated therapy. Observe usual precautions in presence of impaired renal or hepatic function.
Adverse Reactions: Dizziness, drowsiness, lightheadedness, staggering, ataxia and falling have occurred, particularly in elderly or debilitated patients. Severe sedation, lethargy, disorientation and coma, probably indicative of drug intolerance or overdosage, have been reported. Also reported: headache, heartburn, upset stomach, nausea, vomiting, diarrhea, constipation, GI pain, nervousness, talkativeness, apprehension, irritability, weakness, palpitations, chest pains, body and joint pains and GU complaints. There have also been rare occurrences of leukopenia, granulocytopenia, sweating, flushes, difficulty in focusing, blurred vision, burning eyes, faintness, hypotension, shortness of breath, pruritus, skin rash, dry mouth, bitter taste, excessive salivation, anorexia, euphoria, depression, slurred speech, confusion, restlessness, hallucinations, paradoxical reactions, *e.g.*, excitement, stimulation and hyperactivity, and elevated SGOT, SGPT, total and direct bilirubins and alkaline phosphatase.
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REFERENCES:
1. Frost JD Jr: Data on file, Medical Department, Hoffmann-La Roche Inc., Nutley NJ
2. Data on file, Medical Department, Hoffmann-La Roche Inc., Nutley NJ
3. Robinson DS, Amidon EL: Interaction of benzodiazepines with warfarin in man, in *The Benzodiazepines*, edited by Garattini S, Mussini E, Randall LO. New York, Raven Press, 1973, p. 641

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breathes more activity into days and more rest into nights.
Please see summary of full prescribing information on the back of this page.

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Tablets contain 5 mg. (equivalent to 4.1 mg. of free base) or 2.5 mg. (equivalent to 2.05 mg. of free base) of Brethine, brand of terbutaline sulfate.

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Contraindications: Known hypersensitivity to sympathomimetic amines.

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Usage in Pediatrics: Brethine, brand of terbutaline sulfate, tablets are not presently recommended for children below the age of twelve years due to insufficient clinical data in this pediatric group.

Precautions: Brethine, brand of terbutaline sulfate, should be used with caution in patients with diabetes, hypertension, and hyperthyroidism. As with other sympathomimetic bronchodilator agents, Brethine, brand of terbutaline sulfate, should be administered cautiously to cardiac patients, especially those with associated arrhythmias. Although the concomitant use of Brethine, brand of terbutaline sulfate, with other sympathomimetic agents is not recommended, the use of an aerosol bronchodilator of the adrenergic stimulant type for the relief of an acute bronchospasm is not precluded in patients receiving chronic oral Brethine, brand of terbutaline sulfate, therapy.

Adverse Reactions: Commonly observed side effects include nervousness and tremor. Other reported reactions include headache, increased heart rate, palpitations, drowsiness, nausea, vomiting, and sweating. These reactions are generally transient in nature, usually do not require treatment, and appear to diminish in frequency with continued therapy. In general, all the side effects observed are characteristic of those commonly seen with sympathomimetic amines.

How Supplied: Round, scored, white tablets of 5 mg. in bottles of 100 and 1,000 and Unit Dose Packages of 100; oval, scored, white tablets of 2.5 mg. in bottles of 100.
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Librax®

Each capsule contains 5 mg chlordiazepoxide HCl and 2.5 mg clidinium Br

Please consult complete prescribing information, a summary of which follows:

Indications: Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows: "Possibly" effective: as adjunctive therapy in the treatment of peptic ulcer and in the treatment of the irritable bowel syndrome (irritable colon, spastic colon, mucous colitis) and acute enterocolitis.
Final classification of the less-than-effective indications requires further investigation.

Contraindications: Patients with glaucoma; prostatic hypertrophy and benign bladder neck obstruction; known hypersensitivity to chlordiazepoxide hydrochloride and/or clidinium bromide.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. As with all CNS-acting drugs, caution patients against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Though physical and psychological dependence have rarely been reported on recommended doses, use caution in administering Librium® (chlordiazepoxide hydrochloride) to known addiction-prone individuals or those who might increase dosage; withdrawal symptoms (including convulsions), following discontinuation of the drug and similar to those seen with barbiturates, have been reported.

***Usage in Pregnancy:* Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

As with all anticholinergic drugs, an inhibiting effect on lactation may occur.

Precautions: In elderly and debilitated, limit dosage to smallest effective amount to preclude development of ataxia, oversedation or confusion (not more than two capsules per day initially; increase gradually as needed and tolerated). Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider pharmacologic effects of agents, particularly potentiating drugs such as MAO inhibitors and phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions (*e.g.*, excitement, stimulation and acute rage) have been reported in psychiatric patients. Employ usual precautions in treatment of anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation have been reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship has not been established clinically.

Adverse Reactions: No side effects or manifestations not seen with either compound alone have been reported with Librax. When chlordiazepoxide hydrochloride is used alone, drowsiness, ataxia and confusion may occur, especially in the elderly and debilitated. These are avoidable in most instances by proper dosage adjustment, but are also occasionally observed at the lower dosage ranges. In a few instances syncope has been reported. Also encountered are isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent and generally controlled with dosage reduction; changes in EEG patterns (low-voltage fast activity) may appear during and after treatment, blood dyscrasias (including agranulocytosis), jaundice and hepatic dysfunction have been reported occasionally with chlordiazepoxide hydrochloride, making periodic blood counts and liver function tests advisable during protracted therapy. Adverse effects reported with Librax are typical of anticholinergic agents, *i.e.*, dryness of the mouth, blurring of vision, urinary hesitancy and constipation. Constipation has occurred most often when Librax therapy is combined with other spasmolytics and/or low residue diets.

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For the patient with duodenal ulcer,* consider the multiple benefits of

Librax®

Each capsule contains 5 mg chlordiazepoxide HCl and 2.5 mg clidinium Br.

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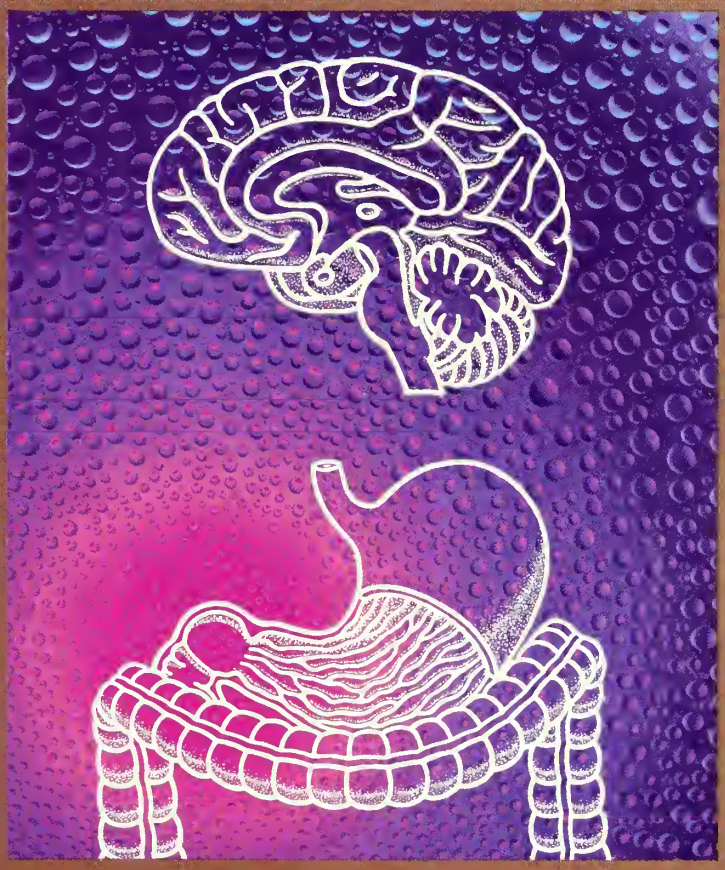

For mild to severe psychovisceral symptoms of duodenal ulcer
Adjunctive Librax®

*is drug has been evaluated as possibly effective for this indication.
ease see brief summary of prescribing information on preceding page.

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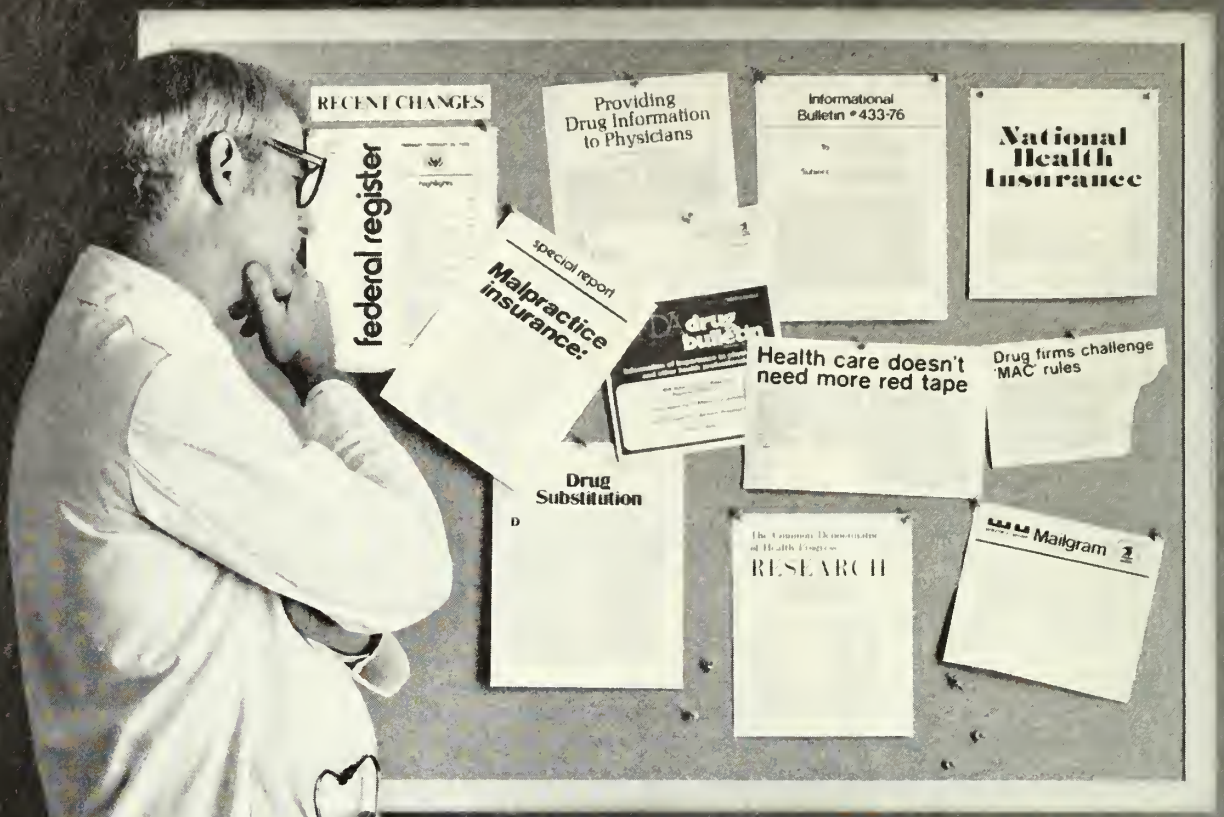
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THERE ARE A LOT OF PEOPLE GETTING BETWEEN YOU AND YOUR PATIENT.

Medicine today is in the spotlight, subjected to all kinds of scrutiny. Your control over patient therapy is being monitored, judged and occasionally abrogated, sometimes by unknown third parties.

The worry is that in the wake of this focus, the relationship between you and your patient will be weakened, without offsetting benefits. Consider three examples:

Drug substitution In most states, pharmacy laws, regulations or professional custom stipulate that your non-generic prescriptions be filled with the precise products you prescribe. But in the last five years, a dozen or more State laws have been changed, permitting the pharmacist in most cases to select a product of the same generic drug to fill any prescription.

Ironically, this dilution of physician control has taken place against a background of growing evidence that purportedly equivalent drug products may be inequivalent, since neither present drug standards nor their enforcement are optimal. In fact, the FDA itself says it has not enforced the same standards for hundreds of "follow-on" products that it had applied to the original NDA approvals. Thus physician control over patient therapy is being eroded with a risk that patients may be exposed to drugs of uncertain quality.

The major advertised claim for substitution is reduced prescription prices for consumers. Yet no documentation of any significant savings has been produced.

MAC Maximum Allowable Cost, MAC for short, is a Federal regulation designed to cut the Government's drug bill by setting price ceilings for drugs dispensed to Medicare and Medicaid patients. Unless the prescriber certifies on the prescription that a particular product is medically necessary, the Government intends to pay only for the cost of the lowest-priced, purportedly-equivalent, generally-available product. The effect of the program may be that elderly and indigent patients will be restricted to products which someone in Washington believes are priced right. Practicing doctors will have little to say about administration of the program, since Government will have absolute authority to make its choices stick.

The drug lag The future of drug and device research depends upon a scientific and regulatory environment that encourages therapeutic innovations. The American pharmaceutical industry annually is spending more than $1 billion of its own funds and evaluating more than 1,200 investigational compounds in clinical research. Disease targets include cancer, atherosclerosis, viruses and central nervous system disorders, among others. But there is a major barrier to the flow of new drugs to your patients: The cost of the research is more than ten times what it was, per product, in 1962; and whereas governmental clearance of new drug applications took six months then, it commonly consumes two years now.

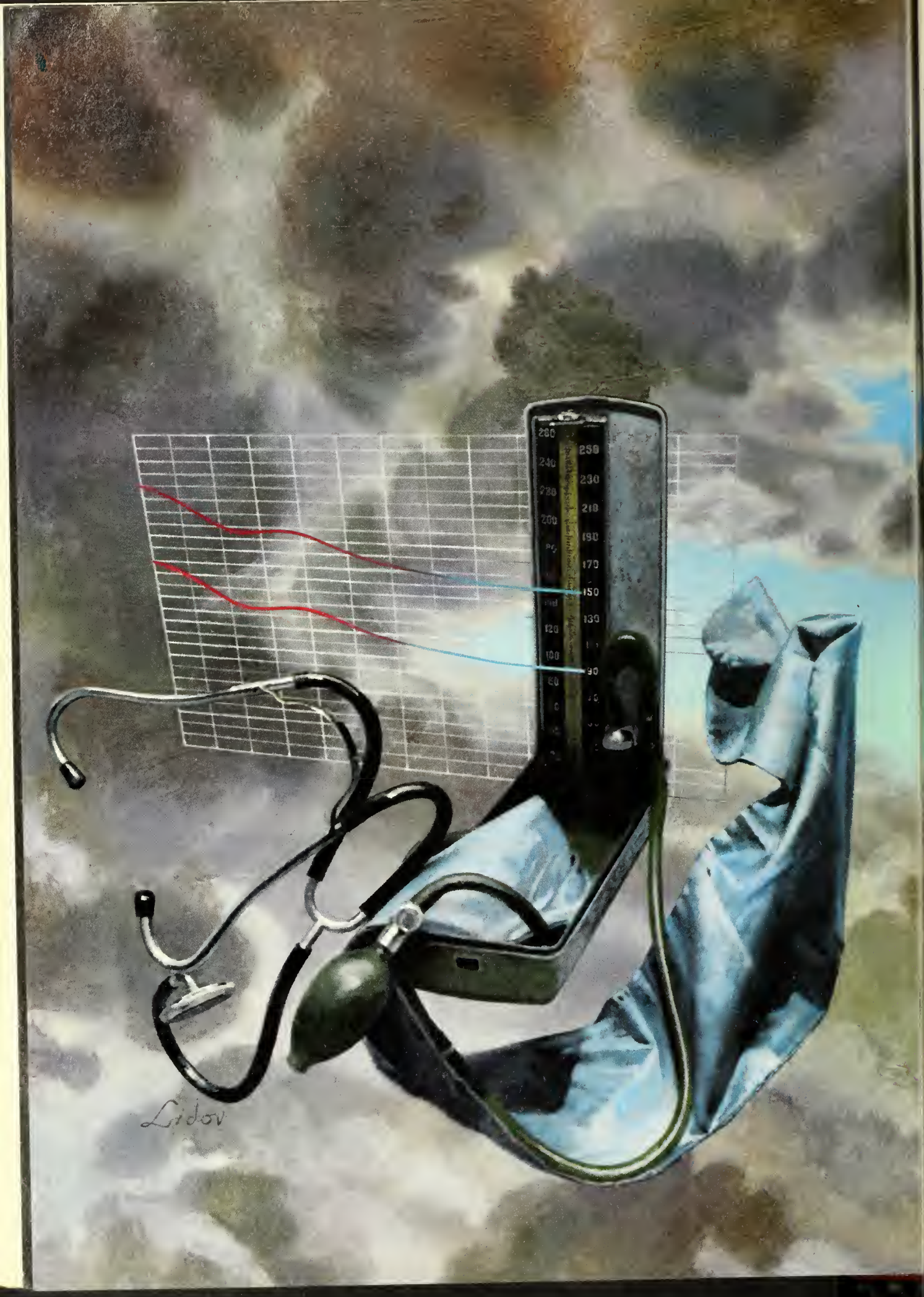
The FDA needs adequate time, of course, to consider data. But it is equally clear that the present approval process contributes to needless delay of needed therapy. That's why the increased efficiency of the drug approval process is vital to all our futures.

If these issues concern you, we suggest that you make your voice heard—among your colleagues and your representatives in State legislatures and in Washington.

It could make a difference in your practice tomorrow.

P·M·A

Pharmaceutical Manufacturers Association
1155 Fifteenth Street, N.W., Washington, D.C. 20005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When choosing a diuretic for day-in-day-out hypertension control with comfortable compliance...

The agent you choose in mild to moderate essential hypertension should offer (1) long-term effectiveness, (2) patient comfort and compliance.

Zaroxolyn offers both.

In one long-term study[1] Zaroxolyn brought moderately elevated (average 161/109 mm Hg) blood pressure down to the range of normotension—and held it there for a year or more.

The investigator noted, "Patient cooperation was surprisingly good for a study of such duration [2½ years]. The once-daily dosage schedule with metolazone [Zaroxolyn] no doubt contributed to patient compliance."

Overall compliance with Zaroxolyn is good—very good. An analysis of controlled clinical studies involving 188 Zaroxolyn patients showed that only eight discontinued therapy because of side effects. That's a discontinuation rate of only 4.3%, and broader clinical experience appears to substantiate this low rate.[2]

Zaroxolyn. For long-term control and comfortable compliance in mild to moderate hypertension.

Recommended initial dosage in mild to moderate essential hypertension–2½ to 5 mg once daily

Zaroxolyn®

(metolazone, Pennwalt)

2½-mg, 5-mg and 10-mg tablets

once-daily antihypertensive diuretic

Before prescribing, see complete prescribing information in the package insert, or in PDR, or available from your Pennwalt representative. The following is a brief summary. **Indications:** Zaroxolyn (metolazone) is an antihypertensive diuretic indicated for the management of mild to moderate essential hypertension as sole therapeutic agent and in the more severe forms of hypertension in conjunction with other antihypertensive agents. Also, edema associated with heart failure and renal disease. **Contraindications:** Anuria, hepatic coma or precoma, allergy or sensitivity to Zaroxolyn. Or, as a routine in otherwise healthy pregnant women. **Warnings:** In theory cross-allergy may occur in patients allergic to sulfonamide-derived drugs, thiazides or quinethazone. Hypokalemia may occur, and is a particular hazard in digitalized patients; dangerous or fatal arrhythmias may occur. Azotemia and hyperuricemia may be noted or precipitated. Considerable potentiation may occur when given concurrently with furosemide. When used concurrently with other antihypertensives, the dosage of the other agents should be reduced. Use with potassium-sparing diuretics may cause potassium retention and hyperkalemia. Administration to women of childbearing age requires that potential benefits be weighed against possible hazards to the fetus. Zaroxolyn appears in the breast milk. Not for pediatric use. **Precautions:** Perform periodic examination of serum electrolytes, BUN, uric acid, and glucose. Observe patients for signs of fluid or electrolyte imbalance. These determinations are particularly important when there is excessive vomiting or diarrhea, or when parenteral fluids are administered. Patients treated with diuretics or corticosteroids are susceptible to potassium depletion. Caution should be observed when administering to patients with gout or hyperuricemia or those with severely impaired renal function. Hyperglycemia and glycosuria may occur in latent diabetes. Chloride deficit and hypochloremic alkalosis may occur. Orthostatic hypotension may occur. Dilutional hyponatremia may occur in edematous patients in hot weather. **Adverse Reactions:** Constipation, nausea, vomiting, anorexia, diarrhea, bloating, epigastric distress, intrahepatic cholestatic jaundice, hepatitis, syncope, dizziness, drowsiness, vertigo, headache, orthostatic hypotension, excessive volume depletion, hemoconcentration, venous thrombosis, palpitation, chest pain, leukopenia, urticaria, other skin rashes, dryness of mouth, hypokalemia, hyponatremia, hypochloremia, hypochloremic alkalosis, hyperuricemia, hyperglycemia, glycosuria, raised BUN or creatinine, fatigue, muscle cramps or spasm, weakness, restlessness, chills, and acute gouty attacks. **Usual Initial Once-Daily Dosages:** mild to moderate essential hypertension—2½ to 5 mg; edema of cardiac failure—5 to 10 mg; edema of renal disease—5 to 20 mg. Dosage adjustment may be necessary during the course of therapy. **How Supplied:** Tablets, 2½, 5 and 10 mg.

References:

1. Dornfeld L, Kane R: Metolazone in essential hypertension. The long-term clinical efficacy of a new diuretic. *Curr Ther Res* **18:** 527-533, 1975
2. Data on file, Medical Department, Pennwalt Prescription Products

PENNWALT

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Her next attack of cystitis may require

the Bactrim 3-system

1. In the urinary tract

Highly effective with fewer recurrences compared to ampicillin or cephalexin

Bactrim has shown high effectiveness not only against *Escherichia coli*, the major uropathogen, but also against most other *Enterobacteriaceae* involved in recurrent UTI. Substantially fewer recurrences have been recorded with Bactrim, as compared to ampicillin or cephalexin.*

Results one month after cessation of treatment

	No. of patients	Antimicrobial therapy	% Negative cultures†
Study 1	80	10-day Bactrim	71.3
	76	10-day ampicillin	56.6
Study 2	60	28-day cephalexin	56.7

Bactrim tablets were used. Bioequivalency studies show one Bactrim DS tablet to be equivalent to two regular strength Bactrim tablets.

*Data on file, Medical Department, Hoffmann-La Roche Inc.
†Criterion: 1000 or fewer organisms/ml urine.

2. In the vaginal tract

It appears from recent studies that the likelihood of recurrent UTI is enhanced by the establishment of large numbers of *E. coli* or other uropathogens on the vaginal introitus.

Bactrim combats uropathogens colonizing the vaginal introitus

Trimethoprim has the distinctive ability to diffuse into vaginal fluid in effective concentrations, thereby reducing or eliminating the number of pathogens in the vaginal introitus, from which they often migrate into the urethra. Bactrim acts to minimize this source of recurrent cystitis in the female.

ROCHE

counterattack

3. In the lower intestinal tract

By its selective action against *Enterobacteriaceae* in the bowel, Bactrim reduces the risk of introital colonization by fecal uropathogens.

Attacks colonic reservoir of uropathogens without significant effect on normal ecologic balance

Bactrim's wide spectrum makes it valuable against most gram-negative bacteria that cause UTI recurrences, yet Bactrim has *no* significant effect on other normal, necessary intestinal flora. Also, Bactrim has rarely been found to cause the intestinal discomfort or fungal overgrowth often associated with broad-spectrum antibiotics.

Bactrim™ DS Double Strength Tablets

Each tablet contains 160 mg trimethoprim and 800 mg sulfamethoxazole.

Just one tablet b.i.d.

To clear her infection* and combat reinfecting organisms

*Due to susceptible strains of *E. coli, Klebsiella-Enterobacter* and *Proteus mirabilis, vulgaris* and *morganii.*

Please see summary of product information on following page.

For recurrent attacks of urinary tract infection in women

the Bactrim 3-system counterattack

- Acts on pathogens at vaginal and lower intestinal sites, in addition to urinary tract; helps eliminate reservoirs of reinfecting organisms
- Antimicrobial synergism plus wide-spectrum effectiveness
- Low incidence of bacterial resistance
- Contraindicated during pregnancy and the nursing period; during therapy, maintain adequate fluid intake, perform CBC's and urinalyses with microscopic examination

Bactrim™ DS

Each tablet contains 160 mg trimethoprim and 800 mg sulfamethoxazole.

Double Strength Tablets

Just one tablet b.i.d. for 10 to 14 days

- Day-and-night action against uropathogens
- B.I.D. regimen encourages patient compliance
- Offers high effectiveness with economy

Bactrim™ Tablets

Each tablet contains 80 mg trimethoprim and 400 mg sulfamethoxazole.

Two tablets b.i.d. for 10 to 14 days

Before prescribing, please consult complete product information, a summary of which follows:

Indications and Usage: For the treatment of urinary tract infections due to susceptible strains of the following organisms: *Escherichia coli, Klebsiella-Enterobacter, Proteus mirabilis, Proteus vulgaris, Proteus morganii* **It is recommended that initial episodes of uncomplicated urinary tract infections be treated with a single effective antibacterial agent rather than the combination.** *Note:* The increasing frequency of resistant organisms limits the usefulness of all antibacterials, especially in these urinary tract infections.

Also for the treatment of documented *Pneumocystis carinii* pneumonitis. To date, this drug has been tested only in patients 9 months to 16 years of age who were immunosuppressed by cancer therapy.

The recommended quantitative disc susceptibility method (*Federal Register*, 37:20527-20529, 1972) may be used to estimate bacterial susceptibility to Bactrim. A laboratory report of "Susceptible to trimethoprim-sulfamethoxazole" indicates an infection likely to respond to Bactrim therapy. If infection is confined to the urine, "Intermediate susceptibility" also indicates a likely response. "Resistant" indicates that response is unlikely.

Contraindications: Hypersensitivity to trimethoprim or sulfonamides, pregnancy; nursing mothers, infants less than two months of age.

Warnings: Deaths from hypersensitivity reactions, agranulocytosis, aplastic anemia and other blood dyscrasias have been associated with sulfonamides. Experience with trimethoprim is much more limited but occasional interference with hematopoiesis has been reported as well as an increased incidence of thrombopenia with purpura in elderly patients on certain diuretics, primarily thiazides. Sore throat, fever, pallor, purpura or jaundice may be early signs of serious blood disorders. Frequent CBC's are recommended, therapy should be discontinued if a significantly reduced count of any formed blood element is noted.

Precautions: Use cautiously in patients with impaired renal or hepatic function, possible folate deficiency, severe allergy or bronchial asthma. In patients with glucose-6-phosphate dehydrogenase deficiency, hemolysis, frequently dose-related, may occur. During therapy, maintain adequate fluid intake and perform frequent urinalyses, with careful microscopic examination, and renal function tests, particularly where there is impaired renal function.

Adverse Reactions: All major reactions to sulfonamides and trimethoprim are included, even if not reported with Bactrim. *Blood dyscrasias:* Agranulocytosis, aplastic anemia, megaloblastic anemia, thrombopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia. *Allergic reactions:* Erythema multiforme, Stevens-Johnson syndrome, generalized skin eruptions, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis. *Gastrointestinal reactions:* Glossitis, stomatitis, nausea, emesis, abdominal pains, hepatitis, diarrhea and pancreatitis. *CNS reactions:* Headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo, insomnia, apathy, fatigue, muscle weakness and nervousness. *Miscellaneous reactions:* Drug fever, chills, toxic nephrosis with oliguria and anuria, periarteritis nodosa and L.E. phenomenon. Due to certain chemical similarities to some goitrogens, diuretics (acetazolamide, thiazides) and oral hypoglycemic agents, sulfonamides have caused rare instances of goiter production, diuresis and hypoglycemia in patients, cross-sensitivity with these agents may exist. In rats, long-term therapy with sulfonamides has produced thyroid malignancies.

Dosage: Not recommended for infants less than two months of age. *Urinary tract infections:* Usual adult dosage—1 DS tablet (double strength), 2 tablets (single strength) or 4 teasp. (20 ml) b.i.d. for 10-14 days.

Recommended dosage for children—8 mg/kg trimethoprim and 40 mg/kg sulfamethoxazole per 24 hours, in two divided doses for 10 days. A guide follows:

Children two months of age or older

Weight		Dose—every 12 hours	
lbs	kgs	Teaspoonfuls	Tablets
20	9	1 teasp. (5 ml)	½ tablet
40	18	2 teasp. (10 ml)	1 tablet
60	27	3 teasp. (15 ml)	1½ tablets
80	36	4 teasp. (20 ml)	2 tablets or 1 DS tablet

For patients with renal impairment:

Creatinine Clearance (ml/min)	Recommended Dosage Regimen
Above 30	Usual standard regimen
15-30	½ the usual regimen
Below 15	Use not recommended

Pneumocystis carinii pneumonitis: Recommended dosage: 20 mg/kg trimethoprim and 100 mg/kg sulfamethoxazole per 24 hours in equal doses every 6 hours for 14 days. See complete product information for suggested children's dosage table.

Supplied: *Double Strength (DS) tablets*, each containing 160 mg trimethoprim and 800 mg sulfamethoxazole, bottles of 100; Tel-E-Dose® packages of 100. *Tablets*, each containing 80 mg trimethoprim and 400 mg sulfamethoxazole—bottles of 100 and 500; Tel-E-Dose® packages of 100, Prescription Paks of 40, available singly and in trays of 10. *Oral suspension*, containing in each teaspoonful (5 ml) the equivalent of 40 mg trimethoprim and 200 mg sulfamethoxazole, fruit-licorice flavored—bottles of 16 oz (1 pint).

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Hearing losses are among the most consistently neglected health problems. Many people with them won't even admit it to themselves, let alone others. A little encouragement may start them thinking about themselves more realistically.

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Average weight loss of 2.15 lbs per week compared in clinical studies against a placebo.

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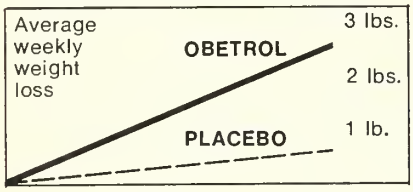
72 CASES 4 WEEKS' RESULTS



Obetrol eases the discomfort of adherence to a restricted diet in individuals who are well motivated to reduce their food intake.

Clinical studies disclose amphetamines to be the most dependable drug in a weight-reduction regimen compared to other anorexigenic agents.

Amphetamines have a significant potential for abuse. In view of their limited short-term anorectic effect and rapid development of tolerance, they should be used with extreme caution and only for limited periods of time in weight reduction programs.

Actions: Amphetamines are sympathomimetic amines with CNS stimulant activity. Peripheral actions include elevation of systolic and diastolic blood pressures and weak bronchodilator and respiratory stimulant action. The anorectic effect diminishes after a few weeks.

Indications: Exogenous obesity, as a short term (a few weeks) adjunct in a regimen of weight reduction based on caloric restriction. For patients in whom obesity is refractory to other measures.

Contraindications: Advanced arteriosclerosis, symptomatic cardiovascular disease, moderate to severe hypertension, hyperthyroidism, known hypersensitivity or idiosyncracy to the sympathomimetic amines. • Agitated states. • Patients with a history of drug abuse. • During or within 14 days following the administration of monoamine oxidase inhibitors, hypertensive crises may result.

Warnings: Tolerance to the anorectic effect usually develops within a few weeks. When this occurs, the recommended dose should not be exceeded in an attempt to increase the effect, rather, the drug should be discontinued. Amphetamines may impair the ability of the patient to engage in potentially hazardous activities such as operating machinery or driving a motor vehicle; the patient should therefore be cautioned accordingly.

Precautions: Caution is to be exercised in prescribing amphetamines for patients with even mild hypertension. Insulin requirements in diabetes mellitus may be altered in association with the use of amphetamines and the concomitant dietary regimen. Amphetamines may decrease the hypotensive effect of guanethidine. The least amount feasible should be prescribed or dispensed at one time in order to minimize the possibility of overdosage.

Adverse Reactions: *Cardiovascular:* Palpitation, tachycardia, elevation of blood pressure. Central nervous system: Overstimulation, restlessness, dizziness, insomnia, euphoria, dysphoria, tremor, headache; rarely, psychotic episodes at recommended doses. *Gastrointestinal:* Dryness of the mouth, unpleasant taste, diarrhea, other gastrointestinal disturbances. Anorexia and weight loss may occur as undesirable effects when amphetamines are used for other than the anorectic effect. *Allergic:* Urticaria. *Endocrine:* Impotence, changes in libido.

Dosage and Administration: Regardless of indication, amphetamines should be administered at the lowest effective dosage and dosage should be individually adjusted. Late evening medication should be avoided because of the resulting insomnia.

1. Narcolepsy: Usual dose 5 to 60 milligrams per day in divided doses.
2. Minimal brain dysfunction:
   a. Not recommended for children under 3 years of age.
   b. Children from 3 to 5 years of age: 2.5 milligrams daily, raised in increments of 2.5 milligrams at weekly intervals until optimal response is obtained.
   c. Children 6 years of age and older, 5 milligrams, once or twice daily, increased in increments of 5 milligrams at weekly intervals. Only in rare cases will it be necessary to exceed a total of 40 milligrams per day.
3. Obesity: Usual adult dose 5 to 30 milligrams per day in divided doses.

Overdosage: Manifestations of acute overdosage with amphetamines include restlessness, confusion, assaultiveness, hallucinations, panic states. Fatigue and depression usually follow the central stimulation. Cardiovascular effects include arrhythmias, hypertension or hypotension, and circulatory collapse. Gastrointestinal symptoms include nausea, vomiting, diarrhea, and abdominal cramps. Fatal poisoning usually terminates in convulsions and coma.

Management of acute amphetamine intoxication is largely symptomatic and includes lavage and sedation with a barbiturate. Experience with hemodialysis or peritoneal dialysis is inadequate to permit recommendations in this regard.

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SF-1. Acid-Base, Fluids, & Electrolytes
SF-2. Echocardiography: Basic Concepts
SF-3. Cutaneous Surgery for the Dermatologist
SF-4. How to Sew (Principles of Suture Technique)
SF-5. Office Gynecology
SF-6. Understanding & Managing Mid-Career Crises for Physicians
SF-7. New Developments in the Treatment of Stroke
SF-8. ENT Emergencies for the Practicing Physician
SF-9. Eye Problems for the Nonophthalmologist
SF-10. Writing for Scientific Journals
SF-11. Update on Practical Antibiotic Therapy
SF-12. Current Techniques in Cardiovascular Nuclear Medicine
SF-73. Cosmetics in Dermatology

Saturday, June 18, 7:30 AM–Noon (-hour course: $50)

SF-13. Basic Life Support—Cardiopulmonary Resuscitation (CPR)

Saturday, June 18, 1:00-5:30 PM (-hour course: $50)

SF-14. Basic Life Support—Cardiopulmonary Resuscitation (CPR)

Saturday, June 18, 9:00 AM–Noon–1:00–5:00 PM & Sunday, June 19, 9:00 AM-Noon (1-hour, 2-day course: $130)

SF-15. Public Speaking Seminar

Saturday, June 18, 8:00-11:00 AM (-hour course: $30)

SF-16. Interpretation of Chest Roentgenograms

Saturday, June 18, 2:00-5:00 PM (3-hour course: $30)

SF-17. Clinical Electromyography for the Referring Physician

Sunday, June 19, 8:00–11:00 AM–2:00–5:00 PM (6-hour, 1-day courses: $60)

SF-18. Electrocardiography: Basic Concepts
SF-19. Diagnosis & Management of Cardiac Arrhythmias
SF-47. Dermatology for Nondermatologists
SF-21. Antibiotic Usage in Pediatrics
SF-22. Primary Treatment of Injuries of the Hand
SF-23. Gynecologic Endocrinology
SF-24. Exercise in the Diagnosis, Prevention, & Rehabilitation of Ischemic Heart Disease
SF-25. Therapy of Sexual Dysfunctions & Disorders
SF-26. Current Bedside Clinics in Neurology

Sunday, June 19, 7:30 AM–Noon–1:00–5:30 PM & Monday, June 20, 7:30 AM-Noon (12-hour, 2-day course: $120)

SF-27. Advanced Life Support—Cardiopulmonary Resuscitation (CPR), Prerequisite: Basic Life Support course; *Required Reading: CPR Advanced Life Support Text* 70034B, $7.50; order through American Heart Association, 7320 Greenville Ave., Dallas, Tex. 75231—make check payable to: American Heart Association

Sunday, June 19, 8:00-11:00 AM (3-hour courses: $30)

SF-28. Liver Disease—New Developments
SF-29. Useful Diagnostic Laboratory Tests in Endocrine Disease
SF-32. Refresher Course in Dermatopathology
SF-70. Diagnosis & Treatment of Fractures of the Lower Extremities

Sunday, June 19, 2:00-5:00 PM (3-hour course: $30)

SF-20. Live Case Presentations for Dermatologists
SF-30. Useful Diagnostic Laboratory Tests in Endocrine Disease

Monday, June 20, 8:00–11:00 AM–2:00–5:00 PM & Tuesday, June 21, 8:00–11:00 AM–2:00 to 5:00 PM (12-hour, 2-day course: $120)

SF-31. Practical Exercises in Emergency Care

Monday, June 20, 8:00–11:00 AM–2:00–5:00 PM (6-hour, 1-day courses: $60)

SF-33. How to Sew (Principles of Suture Technique)
SF-34. Problem Care Seminar on Common Hand Injuries: Basic & Advanced Techniques
SF-35. Respiratory Emergencies in Children
SF-36. Critical Injuries: Recognition & Early Treatment
SF-37. Evaluation & Management of Respiratory Failure
SF-38. Spine & Spinal Cord Injuries: An Update for Primary Care Physicians
SF-39. Peptic Ulcer
SF-40. Diabetes
SF-41. Practice Management Seminar
SF-42. An Overview of Current Psychotropic Drugs

Monday, June 20, 8:00–11:00 AM (3-hour course: $30)

SF-44. Management of Convulsive Disorders: "Fits Are Old—Not So Appraisal or Treatment"
SF-71. Diagnosis & Treatment of Fractures, Dislocations, & Epiphyseal Injuries in Children

Monday, June 20, 1:00-5:30 PM (5-hour course: $50)

SF-43. Basic Life Support—Cardiopulmonary Resuscitation (CPR)

Tuesday, June 21, 8:00–11:00 AM–2:00–5:00 PM (6-hour, 1-day courses: $60)

SF-45. Acid-Base, Fluids, & Electrolytes
SF-46. Echocardiography: Basic Concepts
SF-48. Some Things Old & Some Things New in the Treatment of Rheumatic Diseases
SF-49. New Drugs in Gastroenterology
SF-50. Urologic Pathology
SF-52. Hypertension 1977: A Practical Approach to the Evaluation & Management
SF-53. Common Errors in Emergency Wound Management: Basic & Advanced Techniques
SF-54. Complete Management of Pulmonary Neoplasms
SF-55. Office & Hospital Management of Anorectal Disease

Tuesday, June 21, 7:30 AM–Noon–1:00–5:30 PM & Wednesday, June 22, 7:30 AM-Noon (12-hour, 2-day course: $120)

SF-56. Advanced Life Support—Cardiopulmonary Resuscitation (CPR), Prerequisite: Basic Life Support course; see SF-27 for required reading

Tuesday, June 21, 8:00–11:00 AM (3-hour course: $30)

SF-51. CT Scanning & Neurological Diagnosis: "New Views of the Old Head"
SF-72. Diagnosis & Treatment of Fractures of the Upper Extremities

Tuesday, June 21, 2:00–5:00 PM (3-hour courses: $30)

SF-57. Biofeedback in Muscle Re-Education & Relaxation
SF-58. Toward More Appropriate Utilization of Laboratory Tests: Maximizing Clinical Information from Laboratory Tests

Wednesday, June 22, 8:00 AM–Noon–2:00–5:00 PM (6-hour, 1-day courses: $60)

SF-59. Electrocardiography: Basic Concepts
SF-60. Diagnosis & Management of Cardiac Arrhythmias
SF-61. Pediatric Dermatology
SF-62. Recent Advances in GI Surgery
SF-64. Diagnosis & Therapy of Common Renal Diseases
SF-65. Office Orthopedics for the Nonorthopedist
SF-66. Drug Interactions Relevant to the Primary Care Physician
SF-67. Practical Office & Laboratory Procedures in Allergic Disease

Wednesday, June 22, 8:00–11:00 AM (3-hour course: $30)

SF-63. On Understanding & Treating Dizziness
SF-69. Office Urology

Wednesday, June 22, 1:00–5:30 PM (5-hour course: $50)

SF-68. Basic Life Support—Cardiopulmonary Resuscitation (CPR)

Registration Form

AMA's 126th Annual Convention/San Francisco/ June 18-22, 1977

Please print and return to:

AMA Dept. of Meeting Services, 535 N. Dearborn St., Chicago, IL 60610; or phone: (312) 751-6503.

I am a member of the AMA through the following state medical association: _____ If you are not an AMA member, please add $35 to your total remittance. ($35 fee does not apply to medical students or residents.) Payment must accompany choice of courses (where fees are required) on this registration form.

Advance Registration. To receive your Advance Registration Card, this form must arrive at the AMA by May 20, 1977. (After this date, please register at Brooks Hall CME Registration Desk, San Francisco, California. Your Advance Registration Card will be sent to you on May 27, 1977, unless you request an earlier mailing date.

General Registration. AMA members and their guests, no fee. Nonmember physicians, $35, their guests, $10 per person. Medical students, residents, and Canadian and other foreign physicians, no fee. (Does not include CME course fees.)

CME Course Registration. Please Note: Fee schedule for each item. Insert course numbers of your choice for each day and indicate your order of preference in the space provided. If minimum registration is not attained for your first choice, your alternate choice will be substituted. The course numbers correspond to the listing and fees shown.

All medical students and residents are entitled to a 50% discount on course registration fees ($10 per credit hour is standard rate). Payment must accompany choice of courses requested on this registration form.

Date		Course No.	Fee	Course No.
Sat.	AM	1st Choice	$	2nd Choice
June 18	PM	1st Choice	$	2nd Choice
Sun.	AM	1st Choice	$	2nd Choice
June 19	PM	1st Choice	$	2nd Choice
Mon.	AM	1st Choice	$	2nd Choice
June 20	PM	1st Choice	$	2nd Choice
Tues.	AM	1st Choice	$	2nd Choice
June 21	PM	1st Choice	$	2nd Choice
Wed.	AM	1st Choice	$	2nd Choice
June 22	PM	1st Choice	$	2nd Choice
		Add $35 if Non-Member	$	
		Total	$	

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SEE REVERSE SIDE FOR HOUSING INFORMATION BEFORE COMPLETING FORM BELOW

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AMA Housing Bureau c/o San Francisco Convention & Visitors Bureau
1390 Market Street Suite 260
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126th AMA Annual Convention
June 18-22, 1977
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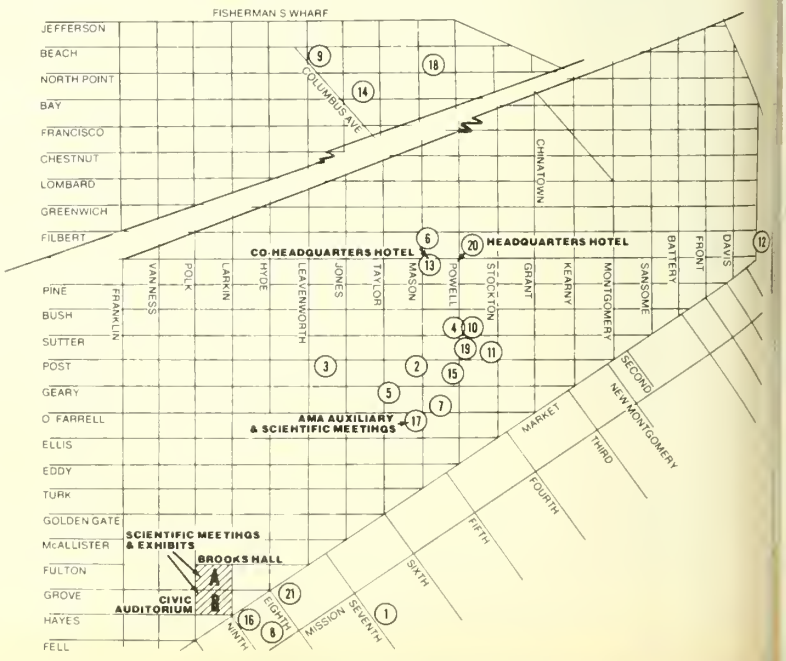
4. Cartwright Hotel	—	$23	$24	—
5. Clift Hotel	—	$60	$60	$150 (1 Bedroom)
6. Fairmont Hotel	Headquarters Hotel • House of Delegates			
7. Handlery Motor Inn	$34-$36	$39-$43	$39-$43	—
8. Holiday Inn-Civic Center	$29	$35	—	$65-$73 (1 Bedroom) $87-$92 (2 Bedroom)
9. Holiday Inn-Fisherman's Wharf	$39-$42	$45-$50	$45-$50	$60 (1 Bedroom)
10. Holiday Inn-Union Square	$42-$45	$48-$51	$48-$51	$81 (1 Bedroom) $132-$162 (2 Bedroom)
11. Hyatt on Union Square	$38-$60	$53-$75	$53-$75	$125-$175 (1 Bedroom) $300-$350 (2 Bedroom)
12. Hyatt Regency San Francisco	$34-$58	$44-$68	$44-$68	$85-$175 (1 Bedroom) $250 (2 Bedroom)
13. Mark Hopkins Hotel	Co-Headquarters • House of Delegates			
14. Ramada Inn-Fisherman's Wharf	$38	—	$46	$80 (1 Bedroom)
15. St. Francis Hotel	$35-$65	$45-$80	$45-$80	available upon request
16. San Franciscan Hotel	$30-$34	$34-$38	$34-$38	$65-$85 (1 Bedroom)
17. San Francisco Hilton	$32-$62	$43-$73	$43-$73	$107-$135 & up (1 Bedroom) $190-$200 & up (2 Bedroom)
18. Sheraton at Fisherman's Wharf	$37-$45	$45-$53	$44-$52	$100 (1 Bedroom) $200 (2 Bedroom)
19. Sir Francis Drake	$32-$54	$40-$60	$40-$60	$145 (1 Bedroom) $185 (2 Bedroom)
20. Stanford Court	Co-Headquarters Hotel • House of Delegates			
21. TowneHouse Hotel	$28-$34	$30-$35	$30-$36	$64 (1 Bedroom) $95 (2 Bedroom)



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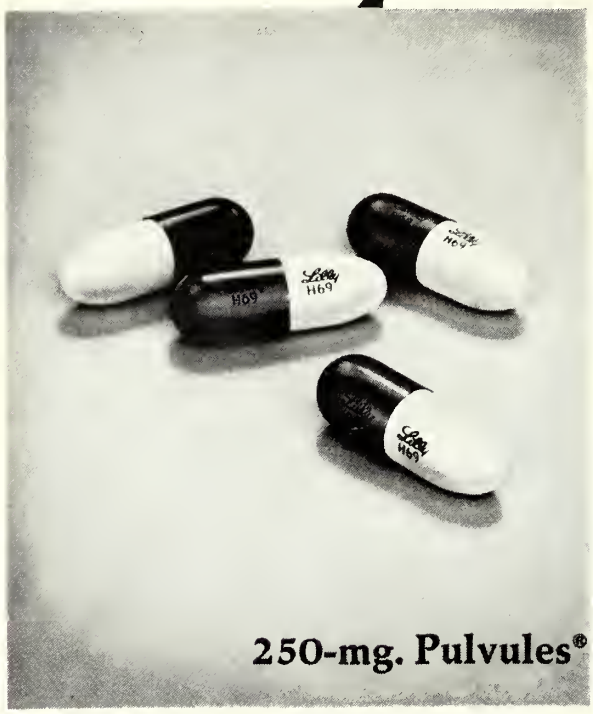

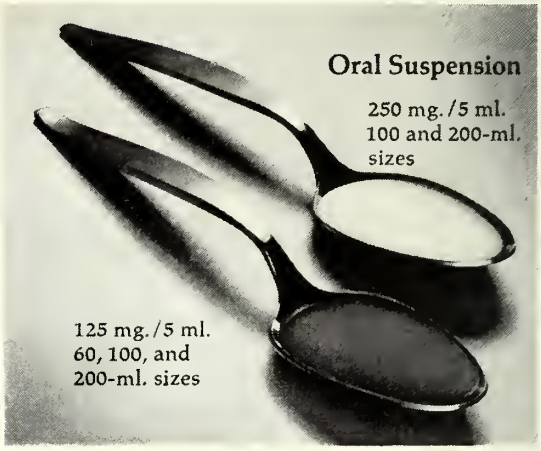

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THE WESTERN
Journal of Medicine

Refer to: Rosove MH: Agranulocytosis and antithyroid drugs. West J Med 126:339-343, May 1977

Agranulocytosis and Antithyroid Drugs

MICHAEL H. ROSOVE, MD, *Santa Monica*

Propylthiouracil and methimazole are used widely in the treatment of hyperthyroid disorders. The most important complication of the use of these drugs is depression of the neutrophilic granulocyte count. Granulocytopenia occurs in about 4 percent and agranulocytosis occurs in about 0.3 percent of treated patients. Although this depression of the granulocyte count is reversible after the drug is discontinued, serious infection frequently accompanies agranulocytosis and accounts for almost all deaths related to the drugs. It is important to be aware of the clinical features of granulocytopenic reactions due to antithyroid drugs.

THE TYPES OF TREATMENT used for the various forms of hyperthyroidism include surgical operation, radioactive iodine and antithyroid drugs. The thiourea derivatives, among which are included thiouracil, methylthiouracil, carbimazole, methimazole and propylthiouracil, have, in addition to radioactive iodine, provided the principal mode of nonsurgical treatment for hyperthyroidism since the institution of their use about 30 years ago. The efficacy of propylthiouracil[1-4] and methimazole[5-7] has been well established. These are the two antithyroid agents in widest use in the United States today, largely because of the relatively low incidence of side effects compared with other agents such as thiouracil.[8-10]

In spite of the efficacy and relative safety of propylthiouracil and methimazole, there are adverse reactions. Among the common adverse effects are skin rashes, urticaria, drug fever and arthralgias.[11] Submaxillary gland enlargement and lymphadenopathy may develop.[12] Hypothyroidism may result if the dosage of drug is not reduced when hyperthyroidism comes under control.[4] Rarely cholestatic jaundice occurs and may be prolonged up to several months.[13-19] Rare lupus-like syndromes include skin ulcers,[20] splenomegaly,[20,21] migratory polyarthritis,[22] pleuritis and pericarditis,[23,24] periarteritis[25] and renal abnormalities.[11,21] Serologic abnormalities include hyperglobulinemia,[11,23] positive lupus erythematosus (LE) cell preparations[11] and the presence of antinuclear antibodies.[11,21,22] Rare hematologic complications of therapy are aplastic anemia,[26-31] pure red cell aplasia[27] and thrombocytopenia.[7,14,16,27]

By far the most frequent adverse hematologic effect of antithyroid drugs, however, and the one of most concern for physicians and patients, is granulocytopenia.[8-16,23,32-45] Most of the common adverse effects have minor significance, and the potentially serious problems of liver involvement

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and lupus-like syndromes are very rare. Agranulocytosis is relatively common, however, affecting about one in 300 patients receiving methimazole or propylthiouracil.[10] It is often accompanied by serious infection and accounts for most of the reported drug related deaths. This paper reviews the clinical features of granulocytopenic reactions due to antithyroid drugs.

Incidence

The terms "granulocytopenia" and "agranulocytosis" are not rigidly defined in the literature, but in general they refer to neutrophilic granulocyte counts in the peripheral blood of less than 1,500 per cu mm and 250 per cu mm, respectively.

There is no apparent age predilection for granulocytopenia induced by antithyroid drugs. Children and adults both are affected. Although the case incidence is higher in females, this probably reflects the higher incidence of hyperthyroid conditions in this group and the resultant exposure to these drugs.[38]

None of the thiourea derivatives have been free of the complication of granulocytopenia. Although thiouracil was an extremely effective antithyroid agent, the primary reason for its discontinuation was the high incidence of granulocytopenic reactions. Van Winkle and co-workers[33] collected reports of 5,745 cases of hyperthyroidism treated with thiouracil and found a 4.4 percent incidence of leukopenia and a 2.5 percent incidence of granulocytopenia. A similar complication rate was noted in the 1,914 thiouracil-treated patients reviewed by Sikkema and associates[37] and the 1,091 patients in Moore's review.[9] Of these 3,005 patients,[9,37] 20 of 63 patients in whom agranulocytosis developed, died, for an overall 0.67 percent chance of death from thiouracil therapy. Clearly, safer alternatives were necessary.

It was felt that propylthiouracil would be an ideal answer when early trials by Astwood and co-workers[1] and McGavack and associates[3] totaling 175 patients failed to show any leukopenic reactions. However, McCullagh and co-workers[34] noted a case among their 110 patients, and subsequently Bartels[39] published his report of 672 patients treated preoperatively with propylthiouracil among which there were seven instances of granulocytopenia and three cases of agranulocytosis. Beebe and co-workers[41] reported on 1,651 collected cases with 19 instances of granulocytopenia and one case of fatal agranulocytosis. McGavack and Chevalley[10] reviewed the subject of leukopenic reactions due to propylthiouracil and methimazole. They found no reactions in patients receiving less than 25 mg of methimazole per day but a 5.4 percent incidence of decreased granulocyte count in those taking 30 mg or more, with one death in about 900 patients. Among the 931 propylthiouracil-treated patients, there was a 2.8 percent incidence of granulocytopenia in those taking less than 150 mg a day, and a 4.5 percent rate in those taking more than 250 mg a day, with one death. The authors concluded that equally effective doses of propylthiouracil and methimazole had a similar rate of complication with a 0.1 percent risk of death due to therapy, and that there was a relationship between dose and risk of granulocytopenia. This relationship was also noted by Wiberg and Nuttall[45] who noted two cases of agranulocytosis among 25 patients receiving 120 mg methimazole per day.

Clinical Features

The clinical features of agranulocytosis due to antithyroid drugs are similar among the various agents. The onset of symptoms is usually abrupt. The commonest presenting complaints are fever, malaise, gingivitis and sore throat. Those patients with granulocytopenia without agranulocytosis usually remain asymptomatic. The alarming suddenness with which symptoms of agranulocytosis may develop is well known;[37] granulocytes may disappear from peripheral blood over two days.[32] Leukopenia may be noted before the development of agranulocytosis.[9,15,36,37] When agranulocytosis develops it generally does so within the first few months of therapy.[10,13,14,35,38-42] It may occur as early as ten days after therapy is begun[10] or may be delayed for up to four months or more.[38,40] Moreover, in patients who previously tolerate a drug well agranulocytosis may develop after repeat courses of therapy with the same drug.[13,36]

The course of symptomatic agranulocytosis may be fulminant with death due to infection occurring within several days.[14,40,41] In patients who recover following discontinuation of the drug, granulocytes reappear in the peripheral blood after a period varying from a few days to three weeks, and the granulocyte count returns to normal shortly thereafter.[8,10,35,38,39,42,46] The course of aplastic anemia due to antithyroid drugs may be prolonged.[29,30]

Among detailed case reports of 25 patients in whom severe drug-related granulocytopenia developed,[8,9,13-16,35,36,38-43,45] other simultaneously oc-

curring drug-induced side effects were infrequently noted. In one patient urticaria was present,[36] in one generalized lymphadenopathy and splenomegaly occurred[8] and in four jaundice developed.[14-16,44]

Bone Marrow

There are no unique diagnostic changes in bone marrow in cases of agranulocytosis due to antithyroid drugs.[12,14,26,29-31,35-37,41-43,45] Except in the rare instances of pancytopenia which are accompanied by an aplastic marrow, only the granulocyte line is affected. The relative number of granulocytes and their precursors may vary considerably from apparent absence to hyperplasia, although a decrease is most common. The marrow morphology is likely to reflect the time during the clinical course at which the specimen is taken.[46] The distribution of granulocytes is frequently "left-shifted," and the appearance of "maturation arrest" is common. Among the 14 studied cases of thiouracil-induced agranulocytosis collected by Sikkema and associates,[37] features compatible with maturation arrest were seen in five. Whether or not the appearance of the marrow in these cases truly represents a maturation arrest is unknown. Excessive utilization of a small pool of granulocyte precursors may produce features of maturation arrest. Moreover, injury incurred at an early stage of granulocyte differentiation may possibly give the appearance of arrest of maturation at a later stage of development.[47] The stage of granulocyte development at which injury is induced by the thiourea derivatives is not known. In a single case[41] a peroxidase stain showed no positive staining cells, suggesting that the defect was imposed at the myeloblast stage or earlier. Morphologic changes have been noted in mature granulocytes[36,43] consisting of cytoplasmic swelling with indistinct margins, and irregularly staining, pyknotic nuclei. The significance of these latter findings is unclear.

Pathogenesis

Information available that might shed some light on the pathogenesis of the granulocytopenia and agranulocytosis related to antithyroid drugs is scanty, and the fundamental questions regarding its mechanism are unanswered. The effect of antithyroid agents on thyroid hormone metabolism has been intensively studied. The most important antithyroid actions are to inhibit the oxidation of iodide to the iodinating species necessary in the synthesis of iodotyrosines and to inhibit the formation of iodothyronines from the coupling of iodotyrosines.[48] Much less is known about the extrathyroidal effects, and specifically the effect on the bone marrow.

Thiouracil readily gains entry into marrow tissue. Its level builds up slowly and eventually exceeds concentrations in the thyroid.[49] In patients with nonthyroidal conditions who were given large doses of thiouracil, high concentrations were found in the marrow.[50] Drug levels within leukocytes may be several times that of plasma.[49]

Oxygen and glucose utilization by leukocytes is affected. Granulocytes from propylthiouracil-treated rats are found to be hypermetabolic with increased oxygen and glucose utilization especially during phagocytosis, an effect independent of thyroid status.[51] However, control leukocytes incubated *in vitro* with propylthiouracil do not show any change in glucose utilization through a wide range of propylthiouracil concentrations.[51] An apparently conflicting observation is that it is possible to show a small but significant decrease in oxygen consumption in granulocytes and to a lesser extent in erythroid cells in the presence of high concentrations of thiouracil.[52]

Very few specific enzymes have been studied in relation to the thiourea derivatives. The cytochrome oxidase activity of thyroid tissue is inhibited by 0.002 mol of thiouracil *in vitro;* however, concentrations up to 0.01 mol do not affect bone marrow[53] although higher concentrations may be inhibitory, raising the question of the significance of the dosage-time factor in some metabolic systems.[37] Leukocytes treated with propylthiouracil show slight decreases in the activity of soluble nicotinamide adenine dinucleotide, reduced form (NADH) oxidase, granule bound nicotinamide adenine dinucleotide phosphate, reduced form (NADPH) oxidase and NADH lactic dehydrogenase.[51] The significance of the preceding observations regarding the development of agranulocytosis is unknown.

Some observations regarding the effect of these agents on nucleic acid metabolism have been made. Thiouracil interferes with ribonucleic acid (RNA) synthesis in slices of rat liver and thymus.[54] Most interesting is that uracil can reverse the inhibition of reticulocyte maturation by thiouracil *in vitro,* suggesting thiouracil is an antimetabolite which may be overcome by adequate concentrations of a necessary substrate.[55] Seemingly contrary to the above is the report that orotic acid

incorporation into RNA of young leukocytes in propylthiouracil-treated rats is increased.[51] However, the same increase is noted in thyroidectomized animals, and therefore this observation may reflect the thyroid state of the animal rather than the effect of propylthiouracil. In one case of marrow aplasia in man due to propylthiouracil,[28] there was no effect of the drug on incorporation of formate or orotic acid into deoxyribonucleic acid (DNA) or RNA, or on uptake of leucine into protein in the bone marrow after recovery.

Specific antibodies are rarely shown. In two cases of aplastic anemia,[28,30] no leukoagglutinins or platelet agglutinins were found. In a patient with propylthiouracil-induced leukopenia, skin ulcers, fever, arthritis, splenomegaly and hyperglobulinemia,[20] immunofluorescent studies with antihuman globulin suggested the presence of an antibody directed to granulocyte cytoplasm. Serum from the patient agglutinated donor granulocytes, and the agglutination was less pronounced with previous incubation of the serum with propylthiouracil. It was suggested that in this patient there was a hypersensitivity disorder with autoimmune leukopenia related to propylthiouracil administration. However, in most cases of granulocytopenia associated with thiourea derivatives, no clinical features suggesting a hypersensitivity disorder are seen. It is likely that agranulocytosis due to antithyroid drugs is not antibody mediated.

Any proposed mechanism relating granulocytopenic reactions to antithyroid drugs will have to take into consideration some clinical observations. First, in only a small percentage of exposed persons does granulocytopenia develop, and even in fewer is there the severe degree of agranulocytosis. Second, the onset of granulocytopenia is frequently delayed. Third, the incidence increases with higher doses. And last, the granulocyte line is usually the only one affected. At present, it seems probable, as previously suggested,[28] that in some persons there is a biochemical susceptibility involving some essential metabolic pathway.

Prevention and Treatment

Unfortunately, there is no way to predict in which patient drug-associated agranulocytosis will develop. It is not clear that following blood counts aids in management since agranulocytosis may develop swiftly. Hence it is most important that patients be warned to discontinue medication and contact their physicians if fever, gingivitis or sore throat develops. Agranulocytosis is usually not presaged by other drug related side effects such as rash, urticaria or arthralgias. Conversely, there is no evidence that patients in whom side effects do develop have an increased risk of developing agranulocytosis.

The proper approach to patients in whom mild to moderate granulocytopenia develops is not clear. In some patients no further depression of the granulocyte count may ever occur and there may be resolution of granulocytopenia despite continued therapy. Amrhein and co-workers[11] reported several patients with propylthiouracil-induced granulocytopenia, and the leukopenia resolved with continued treatment. In half the patients with thiouracil-induced leukopenia reported by Van Winkle and associates,[33] the leukocyte count returned to normal levels in spite of continued therapy. A patient with agranulocytosis due to thiouracil was subsequently given the drug again without complication.[32] Granulocytopenia may be associated with hyperthyroidism, and in these instances the granulocyte count may rise with antithyroid therapy.[45]

Very little information is available concerning the safety of changing therapy to another thiourea derivative in patients with granulocytopenic reactions. In a few patients in whom granulocytopenia developed with propylthiouracil administration, there was no improvement in the leukocyte count with thiouracil or methimazole therapy.[11,38] Two patients who had propylthiouracil-induced agranulocytosis were subsequently given thiouracil. In one, agranulocytosis developed; in the other it did not.[39] Patients may tolerate one or more drugs well and yet a severe reaction to another may develop. A patient with methimazole-induced aplastic anemia had had previous exposure to propylthiouracil with only an urticarial reaction.[26] Another patient was treated with thiouracil for 3 months and with methylthiouracil for 21 months, and then fatal marrow aplasia developed after carbimazole was given for 4 months.[27] Unfortunately, there are inadequate numbers of reported cases and no controlled studies concerning the safety of continued therapy with antithyroid drugs in the presence of granulocytopenia. It would seem wise, however, to be certain of the indication for continued medication, to reduce the dose to the minimum necessary to control hyperthyroidism and to follow blood counts in patients who have significant granulocytopenia.

Once agranulocytosis with overt infection is established, treatment consists of immediate ad-

mission to hospital, discontinuation of the drug, specific antimicrobial therapy, treatment of hyperthyroidism and general supportive measures. Isolation techniques and granulocyte transfusions may be beneficial. In survivors, the granulocyte count will usually return to normal levels in a period varying from a few days to three weeks.

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The Absolute Granulocyte Count in Ascites Fluid

An Aid to the Diagnosis of Spontaneous Bacterial Peritonitis

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The absolute granulocyte count of peritoneal fluid was determined for 98 consecutive patients with ascites in order to assess its value as an early indication of bacterial infection. The absolute granulocyte count was found to be more sensitive and specific than either the total leukocyte count or differential count alone. When the absolute granulocyte count in ascites fluid is greater than 250 per cu mm, then it is likely that infection is present.

SINCE THE clinical manifestations of bacterial peritonitis in patients with preexisting ascites are often subtle or nonspecific, the diagnosis depends upon results of studies of the peritoneal fluid.[1,2] Despite the presence of infection, bacteria are not seen in the Gram-stained ascites fluid sediment in 40 percent of cases,[1] and culture results are not available immediately. Therefore, reliance has been placed upon the leukocyte count as an indication of infection and the need for empiric antibiotic therapy.[1,2] However, the total leukocyte count and the differential count are of limited value since those associated with spontaneous bacterial peritonitis overlap the counts found in ascites uncomplicated by infection.[3,4] To assess the value of the absolute granulocyte count of peritoneal fluid in the evaluation of ascites for the exclusion of bacterial peritonitis, we retrospectively reviewed the case records of 98 consecutive patients in whom studies of ascites fluid had been carried out.

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Patients and Methods

All patients in whom peritoneal fluid studies had been done between February 1, 1973, and January 31, 1975, were identified from the laboratory records of the Veterans Administration Hospital, Dallas, Texas, and their hospital records were reviewed. The clinical, laboratory and histopathologic findings, and the most likely diagnostic condition causing the ascites were recorded. In the absence of histologic confirmation, a patient was regarded as having liver disease if the following findings were present: (1) spider nevi, (2) evidence of portal-systemic shunting—that is, esophageal varices or hepatic encephalopathy and (3) elevated serum glutamic oxaloacetic transaminase, alkaline phosphatase and bilirubin values. Spontaneous bacterial peritonitis was defined as acute peritonitis caused by bacteria in a patient with ascites.[1] The absolute granulocyte

count was determined simply by multiplying the total leukocyte count by the granulocyte percentage of the differential count.

Results

Cause of Ascites

In all, 98 patients were identified in whom ascites was examined on one or more occasions (Table 1). Clinical or histologic evidence of liver disease, which in all cases was attributed to alcohol abuse, was noted in 80. Of these, in 23 there was complicating illness known to alter ascitic fluid (either an infection, pancreatic disease or cancer). In 11 of these, spontaneous bacterial peritonitis was noted. Bacteria were cultured from the peritoneal fluid in nine: Escherichia coli in six, Staphylococcus aureus in one, Streptococcus pneumoniae in one and Clostridia species in one; in the other two, Gram stain of the fluid showed Gram-negative rods, but cultures were negative. In 57 others, only alcoholic liver disease was a cause for the ascites. In 18 patients there was no evidence of liver disease, and in each of these a cause for the ascites was present.

Laboratory Results

The total leukocyte and absolute granulocyte counts of the peritoneal fluid are graphed in Figure 1. The data are arranged so that the results for the 57 patients with uncomplicated alcoholic liver disease (ALD) can be compared with those for the 11 persons with spontaneous bacterial peritonitis (SBP).

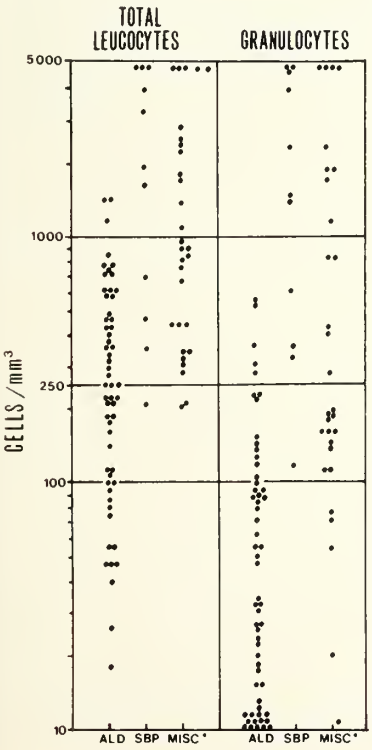

Figure 1.—Ascites fluid cell counts in 98 patients with uncomplicated alcoholic liver disease (ALD), spontaneous bacterial peritonitis (SBP) or miscellaneous conditions.
*See text

TABLE 1.—*Cause of Ascites in 98 Patients*

Cause	*Total*	*Liver Disease*	*No Liver Disease*
Infection			
Tuberculosis-documented	2	0	2
Tuberculosis-presumptive	3	3	0
Spontaneous bacterial peritonitis	11	11	0
Secondary bacterial peritonitis			
Perforated viscus	1	1	0
Mesenteric infarction	3	1	2
Adjacent infection	4	1	3
Pancreas			
Pancreatitis	5	3	2
Pancreatic ascites	3	1	2
Cancer			
Hepatoma	2	2	0
Other	6	0	6
Chronic Hemodialysis Associated	1	0	1
SUBTOTAL	41	23	18
Liver Disease Only	57	57	0
TOTAL	98	80	18

The remaining 30 cases are grouped in the miscellaneous column. This group includes those with tuberculosis (five), secondary bacterial peritonitis (eight), acute pancreatitis (five), pancreatic ascites (three), cancer (eight) or chronic hemodialysis (one). In all but two of these cases (one patient each with cancer and tuberculosis) there were total leukocyte counts less than 250 cells per cu mm. However, only in those patients with secondary bacterial peritonitis (seven of eight), acute pancreatitis (four of five), pancreatic ascites (two of three) or cancer (one of nine) were there absolute granulocyte counts greater than or equal to 250 cells per cu mm. The range, mean and median for the total leukocyte and absolute granulocyte counts are recorded in Table 2. Since these data appear to be nonparametric, it was not possible to derive confidence limits.

TABLE 2.—*Total Leukocyte and Absolute Granulocyte Counts in Uncomplicated Alcoholic Liver Disease (ALD) and Spontaneous Bacterial Peritonitis (SBP)*

	Total WBC		*Granulocytes‡*	
	*ALD**	*SBP†*	*ALD*	*SBP*
Range	15-1,400	110-5,600	10-560	106-5,600
Mean	360	5,500	86	4,716
Median	250	1,971	32	1,470

*57 cases. †11 cases.
‡P = 0.001 - Mann Whitney U Test

The total protein content of the fluid was greater than 2.5 grams per 100 ml in five of the 57 patients with uncomplicated alcoholic liver disease and less than 2.5 grams per 100 ml in the rest. In all patients with spontaneous bacterial peritonitis there were ascitic fluid protein levels less than 2.5 grams per 100 ml. In the miscellaneous group of conditions, the protein value varied from 0.7 to 5.5 grams per 100 ml. In all the patients with pancreatic ascites, tuberculosis or chronic renal failure, there were ascitic fluid protein concentrations greater than 3 grams per 100 ml. Of the six patients with cancer, in three there were ascitic fluid protein levels greater than 2.5 grams per 100 ml and in two there were levels less than 2.5 grams per 100 ml; in one this was not measured.

Discussion

Regardless of the data presented by Burack and Hollister,[5] in many patients with uncomplicated ascites from alcoholic liver disease there are total leukocyte counts in excess of 250 per cu mm. This is well documented in our study as well as in others.[1-4] However, the absolute granulocyte count appears to be more specific. In only five of 57 patients with uncomplicated alcoholic liver disease were there more than 250 granulocytes per cu mm, and in all but one of 11 patients with spontaneous bacterial peritonitis this count was exceeded. In most patients with other types of bacterial infections, such as peritonitis secondary to a localized process, there also were granulocyte counts greater than 250 per cu mm, as was also true in patients with pancreatitis. Persons with pancreatitis can be distinguished with ease from the infected patients, since in the former ascitic fluid amylase values are greatly elevated. As expected, ascites associated with tumor or tuberculosis did not evoke a granulocyte response. Therefore, in the group studied, a granulocyte count greater than 250 cells per cu mm was a relatively sensitive and specific indication of bacterial peritonitis, either spontaneous or secondary to other intraabdominal infections.

In general, these findings support the view of Kline and co-workers[3] and Conn[4] that the leukocyte and differential counts lack specificity in determining presence or absence of infection. However, it appears that valuable information can be salvaged by simply deriving the absolute granulocyte count from these data.

This study also confirms the observation of Sampliner and Iber[6] that an ascitic fluid protein concentration greater than 2.5 grams per 100 ml is more common in uncomplicated alcoholic liver disease than usually appreciated.

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Subtypes of Depression—Diagnosis and Medical Management

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Depression is both a common and a greatly undertreated illness in the United States today. The focus of this review is a definition of the characteristics of four subtypes of depression which appear to be differentially sensitive to four different classes of medications. The tricyclic antidepressants should be used for patients with unipolar depression and vegetative symptoms. Lithium appears to be most effective for bipolar depressives. The monoamine oxidase (MAO) inhibitors are best used for patients with atypical depression. Antipsychotic medications appear to be useful for depressed patients with psychotic symptoms or agitation. Recent pharmacokinetic and biochemical data, including serum lithium levels, plasma tricyclic levels, and the predictive ability of pretreatment urinary 3-methoxy-4-hydroxyphenylglycol (MHPG) levels are also reviewed.

DEPRESSION is both a common and a greatly undertreated illness in the United States today. Recent survey estimates indicate that in any given year 15 percent of adults between the ages of 18 and 74 years may suffer serious depressive symptoms, while only a small percentage of these 20 million persons receive treatment for their illness.[1] Clearly the human suffering and the risk of suicide which accompany this very treatable group of disorders make it imperative for medical practitioners to diagnose and effectively treat this illness. In addition, the cost of evaluating the physical complaints which often accompany depression make it economical, as well as humane, to treat this disorder effectively.

Because most of the medication used to treat depression is prescribed by nonpsychiatrists,[1] it is critical for general practitioners to remain informed of new developments in the psychopharmacological management of depressive illness. Since evidence that this information has not been widely disseminated has recently been accumulated,[2] an updated review of this subject appears indicated. Recent advances in the treatment of depression, as well as massive pharmaceutical advertising in this field, underline further the need for systematic review of the current literature.

The focus of this review will be a definition of the characteristics of four subtypes of depression which are emerging from research literature and which appear to be differentially sensitive to the following medications: tricyclic antidepressants, lithium, monoamine oxidase (MAO) inhibitors and antipsychotic medications. The antianxiety agents and hypnotics will not be discussed because the literature does not support their use in the treatment of depression. Information concerning the diagnosis of depressive subtypes will be in-

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ABBREVIATIONS USED IN TEXT
MAO = monoamine oxidase
MHPG = 3-methoxy-4-hydroxyphenylglycol

cluded in each section, since accurate diagnosis is critical for the selection of the proper psychopharmacological agent. Recent findings concerning the administration of medication will be discussed where pertinent. This article will not discuss those subtypes of depression which appear to be more appropriately treated by various forms of psychotherapy alone. The concomitant use of psychotherapy with antidepressant medication is also beyond the scope of this paper. However, it should be recognized that the proper use of interpersonal support constitutes an important part of a depressed patient's total therapeutic program.

References quoted will be the most comprehensive or recent.

Tricyclic Antidepressants

The literature coscerning the prediction of response to imipramine and amitriptyline has recently been extensively reviewed.[3] These two tricyclics were chosen because they have been used longer than the others and have been utilized in most of the studies with a predictive focus. Several variables have emerged as consistent predictors of response to these medications (Table 1). The presence of insidious onset,[4] weight loss,[5,6] anorexia,[7,8] and middle or late insomnia[4-8] predicted a positive response to both imipramine and amitriptyline. Psychomotor retardation also predicted a favorable response to both drugs[6,7,9-12] while psychomotor agitation consistently predicted a favorable response only to amitriptyline.[8,12] The predictive ability of these so-called "vegetative" symptoms supports the clinical lore that the tricyclics are most effective in the treatment of "endogenous" depressions. Klein[13] has stated that the depressed patients most likely to respond to imipramine therapy are those in whom there is a diminished ability to experience pleasure, and labeled this type of depression *endogenomorphic*. This may be a useful concept for distinguishing these serious depressions from grief reactions, where the pleasure mechanism remains intact. There was also consistent evidence that socioeconomic class variables might be predictive of tricyclic antidepressant response, with upper socioeconomic class predicting a more favorable outcome.[14-17]

Several studies which evaluated the predictive ability of pretreatment urinary 3-methoxy-4-hydroxyphenylglycol (MHPG) levels[18-21] have recently been reviewed.[22] Depressed patients with low urinary MHPG levels respond to imipramine but not to amitriptyline while the converse is true for those with normal or high MHPG levels. While these data appear promising, only small groups of inpatients have been studied to date. The utility of these findings will depend upon the results of larger studies and also upon the ability of depressed outpatients to reliably collect multiple 24-hour urine specimens. Depressed patients with low urinary MHPG levels who responded to imipramine and desipramine also experienced a brightening of mood with a brief trial of dextroamphetamine. It is conceivable that such a trial might be a useful test for the prediction of response to these two medications until the MHPG assay, if proven valuable, is more widely available. Otherwise, stimulants such as amphetamine and ritalin do not appear to be effective treatments for definable depressive subtypes.

Certain patient characteristics predicted an unfavorable response to the tricyclics. The presence of neurotic, hypochondriacal, or hysterical personality traits in depressed patients has consistently predicted that they respond no better to the tricyclics than to placebo.[4-7,9,17,23] Several studies[6,7,23,24] showed that the more previous de-

TABLE 1.—*Indications for Selection of Medications in the Treatment of Subtypes of Depression*

Medication	*Clinical Characteristics*
Tricyclics	*Unipolar depression:* anorexia; weight loss; middle, late insomnia; agitation, retardation
Lithium	*Bipolar depression:* weight gain; hypersomnia; labile mood; recurrent episodes of depression
Monoamine Oxidase (MAO) Inhibitors	*Atypical depression:* well adjusted premorbidly; precipitant; mild, variable depression; phobic anxiety; hysterical features; somatic complaints; restless sleep; fatigue; irritability
	Hysteroid dysphoria: Mood shallow, labile; dependent; histrionic; flamboyant; seductive
Antipsychotics	Psychotic symptoms? Agitation?

pressive episodes a patient had had, the less likely he was to respond to a tricyclic antidepressant. This raises the possibility that perhaps lithium is a more advantageous treatment for patients with multiple, recurrent depressive episodes, as discussed below. Finally, the presence of delusions in depressed patients consistently predicted an unfavorable response to the tricyclics.[12,25-27] Glassman[25,28] recommends electroconvulsive therapy as the treatment of choice for these depressives.

Recent studies[29-33] have suggested the importance of achieving minimum plasma tricyclic levels in order to produce a positive response to these medications. Glassman and co-workers[29] found that 40 percent of depressed patients receiving 3.5 mg per kg of body weight of imipramine fail to achieve therapeutic plasma levels. Gram and associates[30] reported that in only 11 of 24 endogenously depressed patients were therapeutic plasma levels achieved when treatment was carried out with imipramine, 225 mg per day. Based on these findings, it appears that the tricyclic antidepressants should be administered in dosages of at least 150 mg per day. Total daily dosages of 300 mg and more of the tricyclics have been shown to be safe.[34] Clearly the routine use of plasma tricyclic levels would be valuable to clinicians in determining adequate dosage for individual patients as well as drug noncompliance. Because the onset of action of the tricyclic antidepressants is relatively long,[35-37] they should be administered at least three weeks before their effect is evaluated. Once a positive response occurs, administration of these medications should probably be continued for at least six months in order to prevent relapse.[38] There is growing evidence that certain patients may benefit from prophylactic tricyclics indefinitely. The entire dose of these medications may be given at bedtime in order to minimize side effects.

Lithium

The prophylactic value of lithium in the treatment of most types of manic depressive illness is reasonably well established and has been discussed recently.[38,40-45] A number of other studies[46-53] have also evaluated the efficacy of lithium in the treatment of acute depression. There is a growing consensus from these latter studies that lithium is effective in the treatment of certain types of depression (Table 1). Mendels,[54] reviewing the predictors of lithium response, reported that an antidepressant effect of lithium is associated with bipolar illness (episodes of both depression and mania or hypomania), a family history of bipolar illness, an "endogenous" symptom pattern and a number of physiological variables. Kupfer and co-workers[55] found that patients with unipolar depression (those without episodes of either mania or hypomania) who responded to lithium therapy differed from those who responded to administration of tricyclics in having lability of mood, more previous admissions to hospital, a family history of mood swings and a family history of bankruptcy.

Pending confirmation of these latter findings and new evidence in this area, it would seem advisable to treat patients with bipolar depression with lithium and unipolar depressives with one of the tricyclic antidepressants. Bipolar patients can be identified by a history of manic or hypomanic episodes or by a family history of bipolar illness. When this information is unclear, the other variables mentioned above may be used, as well as symptom variables. Detre and associates[56] found that patients with bipolar depression more commonly experienced hypersomnia rather than hyposomnia, and experienced significantly more hypersomnia than did patients with unipolar depression. In addition, this hypersomnia was significantly associated with weight gain and feeling worse in the morning. Patients with unipolar depression, on the other hand, more commonly experienced hyposomnia than hypersomnia. It would appear, then, that hypersomnia and weight gain may be predictive of lithium response while hyposomnia and weight loss are predictive of tricyclic antidepressant response.

Some authors[57-59] have suggested the combined use of lithium and other antidepressants (tricyclics or MAO inhibitors) in the treatment of refractory depressions. These findings are provocative but not conclusive, and warrant further study.[54]

The dosage of lithium prescribed should be determined by serum lithium levels as well as by clinical response and the occurrence of side effects. While different authors recommend different serum levels, an average effective, nontoxic range for acute depression appears to be 0.8 to 1.4 mEq per liter,[52,53] while the optimal prophylactive level is 0.8 to 1.0 mEq per liter.[45] The authors' recent clinical experience suggests that serum lithium levels of at least 1.0 mEq per liter should be achieved before any patient is considered to be a lithium nonresponder. Because of pronounced individual differences in absorption,

distribution and excretion of lithium, dosages ranging from 800 to 3,000 mg per day may be required to achieve these serum levels.[60] Clinical experience suggests that it may be efficacious to administer lithium once or twice a day to some patients, thereby increasing compliance. Once effective, lithium should be administered indefinitely for prophylactic benefit,[40,44] pending additional findings in this area.

MAO Inhibitors

A review of the literature discussing the rational use of the monoamine oxidase (MAO) inhibitors has been published recently.[61] The major indication for use of these agents appears to be the symptoms associated with the diagnosis of *atypical depression.* The original description of this syndrome was by West and Dally in 1969.[62] Since then, a number of studies[63-67] have confirmed that MAO inhibitors are the treatment of choice for this disorder. These patients become depressed after a precipitating stress, having been quite well-adjusted premorbidly. Their depression is mild, varies from day to day, and is often masked by phobic anxiety. Hysterical features are reported to be common during the illness. Unfortunately, these features are not adequately described in this literature. Somatic complaints, restless sleep, fatigue and irritability are also common during the illness. Endogenous symptoms such as weight loss and early morning awakening occur irregularly.

Klein and Davis[35] have described a similar syndrome, which they call *hysteroid dysphoria,* for which MAO inhibitors are also the treatment of choice. These patients are usually females whose mood is shallow and labile, and who depend upon external sources of approval. While they describe their mood as "depressed" they seldom have vegetative symptoms and remain quite active. They tend to be histrionic, flamboyant and seductive. While resembling the hysterical personality, Klein and Davis suggest that these character traits are secondary to a primary affective disturbance. In contrast to the patients with atypical depression, in these patients the personality defects are chronic and, although quite reactive, not precipitated by an overwhelming stress.

As with the tricyclic antidepressants, response to MAO inhibitors is usually delayed and may vary from several days to a few weeks. Outcome appears to be more favorable with increased dosages or with treatment lasting six or more weeks, suggesting a relationship between dose and the timing of clinical response.[61]

Despite concern over the side effects of the MAO inhibitors, particularly hypertensive crisis[68] it appears that they are safe when used with the proper precautions. Tyramine-containing foods as well as pressor drugs should be restricted. The MAO inhibitors should not be given parenterally. Raskin[69] reported that in only three of 110 inpatients treated with phenelzine did the treatment have to be terminated because of serious side effects, and in none for hypertensive crisis, when these precautions were used. A list of precautions for patients receiving MAO inhibitors has been published.[66] The reader is referred to these instructions for his own use in accompaniment with prescription of these underutilized medications.

Several reports[70-72] indicate that the combination of MAO inhibitors and tricyclic antidepressants is safe when used cautiously, and also that this regime may be useful in the treatment of depressions refractory to other modalities. This particular therapeutic approach requires further investigation.

Antipsychotic Medications

Research concerning the efficacy of antipsychotic medications in the treatment of depression has been impeded by disagreement as to the meaning of the term *psychotic depression.* On the one hand psychotic means severe,[73] or endogenous,[9] while on the other it refers to the presence of symptoms such as delusions and hallucinations. This is an important issue, as delusional depressives have been shown to be nonresponsive to tricyclics.[12,25-27] In addition, few studies have addressed themselves to the use of antipsychotic medications in depressed patients. Kiev[74] compared the antipsychotic thiothixene with the tricyclic protriptyline in the treatment of "psychotic depression." Unfortunately, the presence of delusions or hallucinations was not mentioned. Thiothixene was equal to protriptyline in this study, and was the superior treatment for agitation and anxiety. Raskin and associates[9] found that imipramine was superior to chlorpromazine for patients with "psychotic" depression. The presence of delusions or hallucinations was not specified. Chlorpromazine was effective, however, in treating agitation and excitement in the psychotic depressives. Hollister and Overall[10] reported that thioridazine was superior to imipramine for anxious depressed patients. Klein and Davis[35] recom-

mend phenothiazines for the treatment of those who are agitated.

It appears, then, that antipsychotic medications might be useful in the treatment of agitation and anxiety in severely depressed patients. However, these data are far from conclusive with regard to the treatment of choice for these conditions. Similarly, delusional depressed patients have a poor response to tricyclics,[12,25-27] but the treatment of choice is uncertain. While electroconvulsive therapy is known to be effective for this disorder,[25,28] it is possible that antipsychotic medications might be effective as well. Clearly, the use of these drugs in the treatment of depressive disorders, especially those with psychotic symptoms, warrants further study.

Comment

The diagnosis of depressive subtypes based on well-defined criteria is the key to selecting the right drug for the right patient. The current state of the literature indicates that patients with unipolar depression with vegetative symptoms (such as insidious onset, anorexia, weight loss, middle or late insomnia, psychomotor disturbance) should receive tricyclic antidepressants. Patients with bipolar depression should receive lithium and those with atypical depression should receive MAO inhibitors. While it appears that the antipsychotic medications are beneficial for depressed patients with psychotic symptoms or agitation, the literature is unclear about the treatment of choice for these persons. This question clearly warrants further study. Delusional patients appear to be unresponsive to tricyclics and, pending further evidence, should probably be treated with electroconvulsive therapy.

The pharmacokinetic and biochemical studies of the 1970's offer considerable promise for more rational psychopharmacological treatment of depression. Optimal serum lithium levels have been reasonably established, and the development of plasma tricyclic levels promises to be very helpful to the physician in prescribing the proper dosage of these medications for individual patients. Finally, the findings concerning the ability of pretreatment urinary MHPG levels to predict response to the tricyclics, while still inconclusive, may lead to an objective laboratory test very useful to practitioners who treat depressed patients.

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Acute Spinal-Cord Lesions from Diving—Epidemiological and Clinical Features

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The aquatic activity that produces the greatest number of spinal-cord lesions is diving. Persons in the general population at greatest risk are males aged 15 to 19 years. Of the cases identified, 45 percent resulted from diving into a river or stream, 27 percent into swimming pools and 28 percent into lakes, reservoirs or the ocean. Distribution by age differed for the major groups of bodies of water. The incidence of spinal-cord injuries was related to season (spring-summer) and day of the week (weekends). The incidence of injuries was highest in those county areas with the least opportunity for exposure to swimming pools or rivers. Of the injured persons, 60 percent were tetraplegic at hospital admission. The most frequent radiologic finding was wedge fracture. This finding, in the absence of objective evidence that most divers struck the bottom of the water reservoir or a hard object, suggests that hyperventroflexion was the mechanism responsible for injury in most of the cases. Physicians and others should be aware of strategy options for preventing or reducing such injuries.

AMONG the most popular leisure-time activities of Americans are aquatic sports including swimming, diving, scuba diving, waterskiing and surfing. The injuries that may result range from trivial ones to spinal-cord lesions and to death from drowning. The aquatic recreation that produces the greatest number of spinal-cord lesions is diving. In fact, greater than 75 percent of all acute spinal-cord lesions that are recreation-related result from diving.[1] (Recreation-related spinal-cord injuries include those associated with athletics, sporting events, aquatic recreation, hiking [falls] and the like. Such injuries from recreational motoring or hunting are classified as injuries from motor vehicle collisions or firearms.) The neurological lesion is often severe enough to result in permanent tetraplegia.

The incidence and epidemiologic features of spinal-cord lesions from diving have not been reported aside from several clinical descriptions of series of cases. Presented here are the results of a

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study of the incidence of acute traumatic spinal-cord lesions due to aquatic diving among residents of 18 Northern California counties. This paper reports on the methods used in case ascertainment, overall incidence rates, human and environmental factors associated with the injuries, and the clinical features of all incidence and prevalence cases identified.

Methods and Materials

The methods used in case ascertainment for the study of traumatic spinal-cord lesions in 18 Northern California counties have already been presented elsewhere.[1] For completeness, this report recapitulates important methodologic considerations.

Definition of Spinal-Cord Injury and Incidence Criteria

For the purposes of this study, a spinal-cord lesion was defined as an acute traumatic lesion of the spinal cord, including trauma to nerve roots that results in sensory or motor deficit, or both. The diagnosis of spinal-cord injury and description of the resulting deficits were accepted as recorded by an attending physician in the hospital admission or discharge record, autopsy protocol or other medical record. All information used was obtained from existing records, not by interview.

For inclusion as an incidence case, the injury must have occurred in 1970 or 1971 to a usual resident of the 18 prespecified Northern California counties (regardless of place of occurrence or place of treatment of the injury). The years 1970 and 1971 were selected to utilize 1970 United States Census data as a denominator in deriving incidence rates according to sociodemographic factors.

Reference Population and Geographic Region

The population at risk was defined as the usual residents of the 18 Northern California counties, a population (1970 United States Census) of slightly more than 5.8 million persons (29.1 percent of the state's population). The counties involved included Shasta, Tehama, Nevada, Placer and El Dorado (mountain region); Butte, Yuba, Sutter, Yolo, Sacramento, San Joaquin and Solano (central valley region); Contra Costa, Alameda, Marin, San Francisco, San Mateo and Santa Clara (coastal region).

TABLE 1.—*Hospital Admission Indexing Code Numbers and Rubrics Used for Spinal-Cord Injury Case Ascertainment**

*Rubric No.**	*Rubric*
349	Other diseases of spinal cord (mono-, hemi-, para-, quadriplegia)
725	Displacement of intervertebral disk
772.1	Birth injury without mention of cause
805	Fracture and fracture dislocation of vertebral column without mention of spinal-cord lesion
806	Fracture and fracture dislocation of vertebral column with spinal-cord lesion
839	Other dislocation: spine
958	Spinal-cord lesion without evidence of spinal-bone injury
959	Other nerve injury
03	Surgical operations: operations on spinal-cord structures

*International Classification of Diseases, Adapted, 8th Revision.[2]

Method of Case Ascertainment

Case ascertainment involved a systematic, exhaustive review of records, files and reports from all hospitals and coroner's offices in each county and records of the State of California Departments of Health (Crippled Children's Service), Rehabilitation and Industrial Relations (Workmen's Compensation). There were three phases to case ascertainment: (1) review of all hospital admission records (the principal method of ascertainment); (2) examination of all autopsy protocols* for evidence of spinal-cord lesions, and (3) review of all records on file with the State of California Departments of Health (Crippled Children's Service), Rehabilitation and Industrial Relations (Workmen's Compensation) to identify spinal-cord injuries possibly missed in the previous two phases.

Before case ascertainment through examination of hospital admission records, indexing rubrics were examined to determine which could best identify those admitted to hospital with a potential spinal-cord injury. All hospitals used the *International Classification of Diseases, Adapted* (ICDA),[2] the hospital adaptation of ICDA[3] or, to a lesser extent, the *Standard Nomenclature of Diseases and Operations.*[4] Tests of potential rubrics at hospitals led to adoption of a final list of nine hospital admission and discharge rubrics (Table 1). The medical record of each potential case with one or more of these rubrics was examined to determine conformance with the defi-

*California law requires that all persons who sustain an unexpected, sudden, violent, or unattended death shall have a postmortem examination and a coroner's investigation (Section 27491, California Government Code).

nition of spinal-cord injury and whether the incidence criteria were met.

Case ascertainment was begun in October 1972 and completed in January 1974. Several months were devoted to case ascertainment outside the 18-county region to identify persons with a spinal-cord injury who were usual residents of the 18-county region but injured elsewhere. For this purpose, admission records of major hospitals in counties on the periphery of the 18-county study region were used (that is, the remainder of California, western Nevada and southern Oregon). A complete search was made of the files of the State of California Crippled Children's Service, Department of Rehabilitation and Workmen's Compensation, to identify all possible cases which met the criteria of incidence. Autopsy protocols were reviewed from 30 of the most populous counties in California, western Nevada and southern Oregon.

Data on the numbers of swimming pools in each of the 18 counties (limited to the type of pool built in the ground) were obtained from a private commercial firm (personal communication, Baker Advertising and Mailing, 3923 West 6th Street, Los Angeles 90020). Data on the numbers of lakes and reservoirs as well as miles of rivers and streams in the 18-county region were obtained from the State of California Department of Fish and Wildlife.

Results

Epidemiologic Features

Incidence. In all, 45 persons with confirmed acute spinal-cord lesions due to diving were identified from the records reviewed. Twelve did not meet residency and year of injury criteria. The remaining 33 persons among the 5.8 million residents of the 18-county area gave an average annual incidence rate of 2.8 per million population. Incidence was about the same for 1970 and 1971. Incidence by age, sex, racial-ethnic group or type of body of water involved was not related to year of occurrence. The single death (dead on arrival) among the 33 cases gives a fatality rate of 3 percent. (In all 45 cases there were two deaths.)

Age, Sex and Race-Ethnicity. Table 2 gives the numbers and rates of injury by age and sex. With both sexes, peak incidence was from 15 to 19 years of age. Incidence rates were about six times as high for males as for females. Persons in the general population at greatest risk were males aged 15 to 19 years. None of the persons were under thirteen or over 44 years old. At the time of the 1970 United States Census, slightly greater than 12 percent of the population of the study area was Mexican-American, and 7.3 percent was black. On the basis of the percentage distribution of the general population by race-ethnicity, the injuries would have been expected to involve four Mexican-Americans and two blacks. In fact, two Mexican-Americans were identified, but no blacks, a difference which was not statistically significant.

External Cause and Types of Bodies of Water. Incidence cases involved diving, except one somersault into a swimming pool. There were no spinal-cord injuries from waterskiing, surfing or boating. Table 3 gives a distribution according to type of body of water and age of injured person. Of the 33 cases, 15 (45 percent) resulted from diving into a river or stream. Swimming pools were second in frequency (27 percent). Distribution by age differed with each of the major groups of bodies of water. For example, six of the nine injuries in swimming pools involved persons 25

TABLE 2.—*Number and Average Annual Incidence of Spinal-Cord Lesions from Diving According to Age and Sex, 18 Northern California Counties, 1970-1971*

	Sex								
	Male			Female			Both Sexes		
*Age**	*Persons Injured*	*Population at Risk*	*Rate per Million*	*Persons Injured*	*Population at Risk*	*Rate per Million*	*Persons Injured*	*Population at Risk*	*Rate per Million*
10-14	3	286,930	5.2	1	277,077	1.8	4	564,007	3.5
15-19	10	260,408	19.2	3	256,429	5.8	13	516,837	12.6
20-24	4	251,388	8.0	0	265,925	..	4	517,313	3.9
25-34	6	403,437	7.4	1	404,889	1.2	7	808,326	4.3
35-44	5	343,047	7.3	0	349,306	..	5	692,353	3.6
All ages†	28	2,853,297	4.9	5	2,947,653	0.8	33	5,800,950	2.8

*There were no reported cases for persons 0-9 or over 44 years of age for either sex.
†Rates calculated on the basis of the populations of 18 Northern California counties combined.

TABLE 3.—*Number of Persons with a Spinal-Cord Lesion from Diving by Age and Type of Body of Water, 18 Northern California Counties, 1970-1971*

Age	Type of Body of Water: Swimming Pool	River, Stream, or Creek	Lake	Ocean	All Types
10-14	1	3	0	0	4
15-19	2	5	4	2	13
20-24	0	4	0	0	4
25-34	3	2	1	1	7
35-44	3	1	1	0	5
All age groups	9	15	6	3	33

years old or above, whereas 16 of the 21 injuries in rivers, lakes and streams involved persons 24 years of age or younger.

Other Factors. Spinal-cord lesions occurred exclusively in May through September, peaking in the three middle months; 3 in May, 9 in June, 9 in July, 8 in August and 4 in September. There were too few cases for statistical test of any relation between month of injury and age; however, the ratio of observed to expected frequencies was highest for those 25 years old or above injured in May and September (Table 4).

The injuries were not distributed evenly throughout the week. Of the 33 injuries, 12 were on Sundays, 5 on Saturdays, 4 on Mondays, 5 on Tuesdays, 3 on Wednesdays and 2 each on Thursdays and Fridays. Day of occurrence was not related to age (<25, ≥ 25 years).

Injury rates were not calculated by county of residence because the numbers were so low for almost all of the counties. However, incidence was highest (5.9 per million) for the mountain counties, intermediate (4.4 per million) for the central valley counties and lowest (2.2 per million) for the north coastal counties. The ratio of spinal-cord lesions per 1,000 in-ground swimming pools was highest in the mountain counties (8.5 per 1,000 pools), and lowest in the valley and coastal counties (0.5 and 0.2 per 1,000 pools, respectively). It should be noted that the ratio for the mountain counties was based on a single injury per 118 in-ground pools. The ratio of injuries per 1,000 miles of rivers and streams for each of the three areas was highest for the coastal counties (9 per 100 miles) and lowest for the valley and mountain counties (0.3 and 0.2 per 100 miles, respectively). The information available to us gave no data on water depths, or heights and types of dives.

Although the injuries were too few for a statistical test of significance, excess numbers of persons with tetraplegia were associated with diving into a lake, a quarry or the ocean, and excess instances of persons with tetraparesis were associated with diving into swimming pools (Table 5). Similarly, no statistical test could be made of association between age and neurologic impairment levels since three of six cells (Table 6) had expected frequencies of less than five. However, the number of tetraplegics was higher than expected for those less than 25 years of age.

Clinical Features

The spectrum of neurologic injuries observed in all 45 cases identified (33 incidence, 12 prevalence) varied from no sensory and minimal motor deficit to complete sensory motor tetraplegia. Three patients with fractures of neural arches of C1-4, wedge fractures of C5 and subluxation of C2-3 and C3-4 were neurologically intact on admission, although all had severe paresthesias at the time of injury. Three patients with only minimal motor weakness of one upper extremity had fractures of neural arches of C5 and C6 and wedge fracture of C6. Ten patients had clinical features of acute central cervical cord syndrome with various degrees of sensory and motor loss. A total of 27 patients (21 <25 years of age and 6 ≥ 25 years of age) were completely tetraplegic at admission, and only 1 of these showed func-

TABLE 4.—*Number and Ratio of Observed to Expected* Frequencies of Spinal-Cord Lesions from Diving by Month of Occurrence and Age, 18 Northern California Counties, 1970-1971*

Age Group (years)	Month of Occurrence: May	June	July	August	September	Number Observed, All Months
<25	0.5	1.1	0.9	1.6	0.4	
OBS/EXP	(1/1.9)	(6/5.7)	(5/5.7)	(8/5.1)	(1/2.5)	21
≥ 25	1.8	0.9	1.3	0.0	2.0	
OBS/EXP	(2/1.1)	(3/3.2)	(4/3.2)	(0/2.9)	(3/1.5)	12
Number observed, all ages	3	9	9	8	4	33

*Based on row×colum÷total number observed.

tional neurologic return and achieved independent ambulation. Of the 27 patients with tetraplegia, there were two physiologic transections of the spinal cord at C4, fourteen at C5, ten at C6 and one at C7. The distribution of locations of transections of the spinal cord was not related to age of the patient or type of body of water. Two patients were admitted in a comatose state with flaccidity, areflexia and tetraplegia possibly secondary to intracranial injuries. These two patients died two and four days, respectively, after hospital admission, and results of autopsy showed bilateral cortical softening, severe maceration of the spinal cord, and fracture dislocation of C3 on C4 and C5 on C6.

Of 13 patients with bradycardia (pulse rate 60 per minute or below), hypothermia and hypotension, there was functional return in only one; the others remained tetraplegic. Those 13 patients with a systolic pressure of 100 mm of mercury or below, with or without bradycardia, also remained tetraplegic.

Most of these patients reported difficulty in breathing, and had been rescued by persons nearby at the time of injury. Only three of these patients had scalp lacerations, suggesting that they struck the bottom of the water reservoir or hard objects.

Two patients with no previous history of peptic ulcer disease developed stress ulcers four to six weeks after the injury, and one of these developed perforation of a duodenal ulcer.

The Queckenstedt test was carried out on six patients. Three in whom there was a positive result were found to have a contused or macerated spinal cord on laminectomy. In one in whom test results were equivocally positive, the spinal cord was reported to be edematous. Those four patients remained tetraplegic. As to the two patients with negative results on a Queckenstedt test, one had acute central-cord syndrome and the other had minimal motor weakness of one upper extremity.

Radiologic Findings. All 45 patients had injury to the cervical spine. None had an injury to the thoracic or lumbar spine. Radiographic evidence of osteoarticular injury was detected in 44 of the 45 patients. The patient in whom there was no radiographic evidence of osteoarticular injury was found on autopsy to have a crush fracture of C3 vertebral body with subluxation on C4. In all, there were 56 vertebral-body fractures in 40 pa-

TABLE 5.—*Number of Persons with a Spinal-Cord Lesion from Diving by Functional Impairment Level and Type of Body of Water, 18 Northern California Counties, 1970-1971*

	Impairment Level						
	Tetraplegia Number*		*Tetraparesis Number*		*Other Neurologic Deficit Number*		
Type of Bodies of Water	*Observed*	*Expected†*	*Observed*	*Expected*	*Observed*	*Expected*	*All Levels Total*
Swimming pool .	1	(4.1)	5	(2.7)	3	(2.2)	9
River/stream ...	7	(6.8)	5	(4.5)	3	(3.6)	15
Lake/ocean	7	(4.1)	..	(2.7)	2	(2.2)	9
All types	15	(15.0)	10	(9.9)	8	(8.0)	33

*Includes one in-hospital death.

†Expected values based on column total×row total÷total number of cases (e.g., 15×9÷33=4.1).

TABLE 6.—*Number of Persons with a Spinal-Cord Lesion from Diving by Functional Impairment Level and Age, 18 Northern California Counties, 1970-1971*

	Impairment Level						
	Tetraplegia Number		*Tetraparesis Number*		*Other Neurologic Deficit Number*		
Age Group	*Observed*	*Expected†*	*Observed*	*Expected*	*Observed*	*Expected*	*All Levels Total*
<25	12*	(9.5)	5	(6.4)	4	(5.1)	21
≥25	3	(5.5)	5	(3.6)	4	(2.9)	12
All age groups.	15	(15.0)	10	(10.0)	8	(8.0)	33

*Includes one in-hospital death.

†Expected numbers calculated on the basis of column total×row total÷total number of cases (e.g., 15×21÷33=9.5).

TABLE 7.—*Osteoarticular Injuries from Diving According to Vertebral Level, 18 Northern California Counties, 1970-1971*

Fractures			Luxations		
Level	*Vertebral Body*	*Neural Arch*	*Level*	*Subluxation*	*Dislocation*
C1	..	1	C1/2	1	..
C2	..	2	C2/3	1	..
C3	3	2	C3/4	4	..
C4	8	2	C4/5	7	2
C5	28	10	C5/6	11	..
C6	15	3	C6/7	3	2
C7	2	..			
TOTAL	56	20		27	4

TABLE 8.—*Number of Persons Sustaining Wedge Fractures from Diving According to Vertebral Level and Types, 18 Northern California Counties, 1970-1971*

	Number of Persons with at Least One Wedge Fracture			
Vertebral Level of Fracture	*One Wedge Fracture*	*Two Wedge Fractures*	*One Wedge Plus Additional Fracture*	*Two Wedge Plus Additional Fracture*
C3	2	..	..	..
C4	0	..	..	..
C5	8	..	..	..
C6	4	..	..	..
C3-4	..	1	..	..
C4-5	..	3	3*	..
C5-6	..	6	1	1*
All levels	14	10	4	1

*Includes additional burst fracture.

tients (Table 7). A total of 16 patients had fractures at two levels, and all the fractures were of adjacent vertebral bodies in continuity. In 24 patients there was fracture at one level only. More older persons ($\geq$25 years) than expected had a fracture at a single level of the cervical vertebrae ($x^2=6.45$, $p=0.01$). Excess numbers of patients with fractures at two levels of the spine were associated with dives into rivers and lakes ($x^2=3.95$, $p=0.05$). Of the 56 vertebral-body fractures, there were 40 wedge, 11 burst and 5 teardrop fractures. The type of vertebral body fracture was not associated with the age of the patient or the type of body of water. In 12 patients there were fractures of the posterior elements or neural arches. In 11 of the patients with fractures of the neural arch there also were associated vertebral-body fractures.

Wedge fracture was the most common type of osteoarticular injury. There were 40 wedge fractures in 29 patients. In 14 of these patients there were single wedge fractures and in 10 two wedge fractures. Four patients had a wedge fracture and a burst fracture in the adjacent vertebral body. One patient had two wedge fractures and a burst fracture in the adjacent vertebral body. The distribution of wedge fractures by vertebral level is given in Table 8. For those with a single wedge fracture, the most common level was the C5 vertebral body. For those with two wedge fractures the C5-6 vertebral bodies were most commonly involved.

There were 25 patients with subluxations at various levels. In addition, there were 4 patients with dislocations of the cervical vertebrae (Table 7). Of the 29 patients with subluxations and dislocations, 28 also had a fracture of a vertebral body or of posterior processes of a vertebra.

Myelograms were carried out on eight patients. Three patients with evidence of myelographic block had a swollen, contused, or macerated cervical spinal cord at the time of operation, and all three remained tetraplegic. Two other patients with myelographic block had a normal-appearing spinal cord on laminectomy, and only one had a functional neurologic return. Three patients with no myelographic defect had central cervical-cord syndrome, and two of the three had excellent neurologic recovery.

Management. Initially, all patients with radiologic evidence of injury to the cervical spine were immobilized and Vinke, Crutchfield, or Cone-Barton tongs were applied for skull traction. Five patients were placed in a Halo body cast without any complication. Decompression laminectomy was carried out on nine patients on the day of injury, and on one patient four days after the injury. Three of the laminectomies were done concomitantly with posterior fusion and wiring. In one patient anterior interbody fusion was done, in addition to laminectomy and posterior fusion, and in another patient who had a laminectomy on the first day, anterior fusion was done because of instability nine weeks later. One patient who had made good recovery following central-cord syndrome had posterior fusion done 12 weeks later because of the persistent instability. Anterior decompression and interbody fusion by Cloward or Smith-Robinson technique were carried out on 12 patients: on seven within one week of the trauma, and on five from 2 to 16 weeks following the injury.

Correlation of Radiographic Findings and Neurologic Return

Radiographic abnormalities of the cervical spine are of little significance in the absence of

neurologic deficit. Hence, the different types of osteoarticular injuries were compared with neurologic recovery of residual deficit.

Eleven burst fractures were present in nine patients, associated with variable degrees of subluxations in eight of them. Teardrop fractures were present in five patients. Three of them had central-cord syndrome and made an excellent recovery, and the other two had second- and third-degree subluxation, with complete tetraplegia that remained unchanged on discharge from hospital.

Forty wedge fractures were seen in 29 patients. Eighteen of these patients remained tetraplegic. Three of four patients with wedge and burst fractures at different levels remained tetraplegic. One patient with a wedge and teardrop fracture at two levels also remained tetraplegic.

Of 16 patients with fractures of two vertebral bodies, 12 had complete tetraplegia. Of these 12 patients, there was functional recovery in only one.

Dislocation or third-degree subluxation was present in four patients; all were tetraplegic. Their neurologic status remained unchanged on hospital discharge. Of 24 patients with subluxation, 22 had associated fractures of vertebral body or neural arch, or both.

Functional Impairment

Of the total 45 patients, six had minimal sensory or motor deficit and within a week were free of any detectable neurologic abnormality. Ten patients with acute cervical central-cord syndrome showed good improvement, and all but one were independent in their activities of daily living 6 to 12 months after the injury. Five of these still had a mild residual sensory and motor loss. Hyperreflexia and positive Babinski sign persisted in all these patients as long as they were followed. In all, 27 patients were tetraplegic at admission, and their impairment remained unchanged except that one patient showed some functional return and was ambulatory with crutches. Two patients died as a result of complications from intracranial injury, and in both there was evidence of cervical spinal-cord maceration on autopsy.

Discussion

The National Institutes of Health have estimated that the cost to society of spinal-cord injury is second only to that of mental retardation, among the neurologic and sensory disorders.[5] Of particular significance in this respect are acute traumatic lesions of the spinal cord as a result of diving, since these injuries always involve the cervical spine and the resulting neurologic deficit, if permanent, is tetraplegia. The actual incidence of spinal-cord lesions in the United States from diving injuries is not known. Burke[6] reported that 8 percent of traumatic spinal-cord lesions in Australia resulted from diving. Kewalramani and Taylor[7] found that 18 percent of spinal column injuries over four years were from diving. This percentage included those with spinal-column injury with and without a spinal-cord lesion. Of the 619 spinal-cord lesions identified in the present study, 5.3 percent were from diving, producing an average annual incidence of 2.8 per million population. Projected nationally, this rate indicates an annual total of 600 to 650 spinal-cord injuries due to diving. This range may be an underestimate because many drownings may have resulted from paralysis from spinal-cord injury. A more thorough postmortem examination of persons who have drowned for evidence of spinal-cord damage could provide information on this question.

Spinal-cord injuries from diving occur mostly among the young. Greater than 51 percent of the cases occurred among teenagers. The number of persons exposed to the risk of injury in diving by age and sex is unknown. Nonetheless, the tragic consequences include a lifetime of permanent disability for a substantial number of young people.

Interestingly, only one of the 15 cases with tetraplegia resulted from diving into a swimming pool. In northern California in 1970 and 1971, there were about 35,500 in-ground public or private swimming pools. In the mountain counties, with only 118 pools, there was one case of spinal-cord injury. The frequencies of diving-related spinal-cord lesions in the valley counties (with about 6,500 pools) and the coastal counties (with almost 29,000 pools) were substantially lower than expected. Although the ratios of injuries per 1,000 pools were based on a total of only nine cases, they suggest highest risk associated with least opportunity of exposure.

Of 15 cases of tetraplegia, 14 resulted from diving into rivers, streams, lakes or the ocean. The numbers of lakes or reservoirs and the numbers of miles of rivers, streams and canals were selected as indication of potential exposure to injury. The ratio of injury was highest in counties with the least opportunity for exposure (coastal counties) and lowest in those counties with the

greatest opportunity for exposure based on number of miles of rivers and the like.

The anatomical site of injury in all cases was the cervical spine. In almost 60 percent of the 45 cases identified, the patients were still completely tetraplegic at hospital discharge. The two patients who died because of associated head injury also had destruction of the cervical spinal-cord which would have resulted in tetraplegia.

Information in some of the medical records indicated that patients had underestimated the depth of water, but only three patients had objective evidence (scalp laceration or hematoma) of having struck the bottom of a water reservoir or a hard object. Lack of functional recovery had a 96 percent correlation (26 of 27 cases) with complete sensory or motor tetraplegia at admission; these patients remained permanently paralyzed. All ten patients with acute cervical central-cord syndrome had significant functional return. The other equally important predictor of neurologic outcome with a 92 percent correlation (12 of 13 cases) was impairment of autonomic function at admission, that is, bradycardia, hypothermia or hypotension. Radiographic abnormalities were less reliable predictors of functional return than were clinical findings at admission. All the same, in most of the cases, fractures at two levels of the cervical spine or burst fractures and dislocation were suggestive of severe and permanent neurologic deficit.

Wedge fractures are generally accepted to be flexion injuries to the vertebral body. Sarpyener[8] postulated that severity of wedging was directly related to the weight of the diver, height of the dive and depth of the water reservoir. This conclusion was not based on experimental data, and, unfortunately, we have no data to confirm or refute this conclusion. Flexion forces in combination with rotary motion would rupture the posterior ligament complex or, without rupture, cause fracture of tips of the spinous processes in addition to wedge fracture. The present series included 29 patients with one or more wedge fractures. In diving it is the combination of flexion and vertical compressive forces over the cervical spine that results in wedge, burst and teardrop fractures, and subluxation or dislocation of vertebrae depending upon the degree of initial flexion of the spine at the time the person contacts the water surface. The angle of projection, velocity of mass center and angular momentum are established in the takeoff of the dive.[9] These factors play a major role in determining the success of the dive, and the alertness and expertise of the diver can modify these factors considerably. Although alcohol or other drugs would probably affect alertness of the diver, no information was available on the use of alcohol or other drugs preceding the injuries incurred.

Burke[6] concluded from the high percentage (88 percent) of burst fractures in diving activities that these were incurred from hitting the bottom of the water reservoir. In the present series, however, only 20 percent of the fractures were burst fractures, with the other 80 percent being wedge and teardrop fractures. Of the three patients who had objective evidence (scalp lacerations) of having struck the bottom of a water reservoir, only two had radiologic evidence of injury: wedge and burst fractures at two levels. This finding would support our hypothesis that hyperventroflexion was the mechanism responsible for injury in most of the cases. Because of the customary slight flexion of the neck in diving, impact with the water surface tending to counteract the momentum of the falling body, would cause hyperventroflexion or hyperretroflexion, depending on the angle of entry into the water, perhaps being great enough to produce the variety of fractures reported *without* any collision with the bottom or hard objects.

About 80 percent of the patients noticed an inability to move the upper and lower limbs immediately after the injury and also reported difficulty in breathing. All were removed from the water by other persons. Most would probably have drowned if not rescued. Many persons who participate in saving lives following diving injury probably have no knowledge of the water-rescue procedures that would be proper when the spinal cord may have been injured. Conventional water-rescue procedures need to be revised in the light of possible cervical spinal-cord injury in diving. Improper moves could aggravate the severity of injury.

The problem of spinal-cord injuries should be examined from an etiologic perspective as well as anatomic and pathologic points. Spinal-cord injuries from diving result from the forces produced in the energy exchanges that result from impacts with the surface of the water or with hard objects or structures in or under it. Haddon[10] has identified a series of strategy options for reducing losses from energy exchange and related injuries such as drowning, an injury produced by inter-

ference with normal energy exchange. Drawing on Haddon's analysis, some options for reducing losses from diving include:

- Prevent the aggregation of water suitable for diving or attempted diving (for example, do not build swimming pools).
- Reduce the amount of energy marshaled (to reduce the heights of diving boards for swimming pools would be one preventive tactic illustrating this option).
- Prevent (or modify the rate of) the release of the energy of the diver on the board (preventing the untrained from using high boards and eliminating shallow water reservoirs are examples of tactics for this option).
- Separate populations at risk and opportunities (places) for diving (locating hazardous bodies of water far away and fencing them illustrate this option).
- Modify the contact surface or basic structure (two important tactics involve softening the bottoms of swimming pools or removing rocks, pilings or other hard obstacles from lakes, rivers and oceans where swimming and diving are practiced or are likely to occur).
- Strengthen divers to make them less susceptible to excess energy delivered to the body in a dive (muscle strengthening exercises are a tactic illustrating this option).
- Increase the availability, speed and competence of emergency medical care and transport (training in techniques to ensure nonaggravation of existing spinal-cord damage during procedures to prevent drownings, or during emergency transport is one tactic that illustrates this option).
- Increase the availability of reparative and rehabilitative measures to stabilize the injury and restore injured persons to maximum functional status.

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Germ Cell Tumors of the Testes

Most malignant testicular neoplasms are of germ cell origin. They are divided into five basic types: seminomas, embryonal carcinomas, teratocarcinomas, adult teratomas and choriocarcinomas. Clinically they may present as an enlarging testicular mass, or with symptoms resulting from metastases or hormonal secretions. The treatment of choice for patients with seminomas is orchiectomy, followed by radiation therapy. This combination results in an 80 to 100 percent five-year survival rate in patients with nonmetastatic or locally metastatic disease. The treatment of nonseminomatous germ cell tumors is more controversial. An aggressive approach, however, with retroperitoneal lymph node dissection and adjuvant chemotherapy has resulted in an overall 78 percent survival rate. Several placental and fetal proteins are secreted by these tumors. Two of these, human chorionic gonadotropin and alpha-fetoprotein, have been shown to be useful for the diagnosis of these neoplasms, for following the disease activity during therapy and for detection of recurrences.

GLENN D. BRAUNSTEIN, MD:* Despite their relative infrequency, testicular neoplasms are among the most interesting tumors to cell biologists, pathologists and endocrinologists. Because approximately 95 percent of these tumors are of germ cell origin, the following discussion will focus on the pathologic, clinical and humoral manifestations of germ cell tumors of the testes.

Thirty years ago, the first widely accepted classification of these tumors was developed by Friedman and Moore.[1] It is therefore appropriate at this time to have Dr. Nathan B. Friedman discuss the classification and pathogenesis of testicular germ cell tumors.

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Pathology of Testicular Tumors

NATHAN B. FRIEDMAN, MD:† Most investigators[1-4] of germ cell tumors recognize that these neoplasms, despite their pleomorphism, manifest only a few basic histologic patterns. These patterns and their relative frequencies[5] are the seminomas (germinomas) (33 to 50 percent), embryonal carcinomas (20 to 33 percent), teratocarcinomas (10 to 33 percent), adult teratomas (10 percent) and choriocarcinomas (2 percent). The embryonal carcinomas, which are the least homogeneous group, include several distinct subtypes: trophoblastic, embryoid, endodermal sinus (yolk sac) and other subsets yet to be identified. The occurrence of all of these subtypes in complex combinations in some of the growths has obscured the basic simplicity of their interrelations. Most

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ABBREVIATIONS USED IN TEXT

AFP = alpha-fetoprotein
CEA = carcinoembryonic antigens
HCG = human chorionic gonadotropin

of these combinations can be classified by the term "teratocarcinoma."

There is general agreement that the adult teratomas result from undifferentiated elements developing into adult tissues just as the tissues and organs of the embryo emerge from embryonic epithelium during normal development. It is also accepted that choriocarcinoma develops as a manifestation of trophoblastic differentiation. The development of other extraembryonic tissues accounts for the formation of Teilum's endodermal sinus (yolk sac) carcinoma[2] and its infantile homologue.[6] The term "teratocarcinoma" was suggested to include growths that combined teratoid structures with carcinomatous ones, whether the latter were embryonal, seminomatous, trophoblastic (but short of true choriocarcinoma) or combinations of these types.

It is about the nature of the seminoma and its transformation into embryonal carcinoma that most of the controversy still exists. The seminoma cell was recognized as a specific cell type some time ago, but was thought to be a homologue of one of the elements of the seminiferous epithelium. The differences in the appearance and behavior of these monocellular growths from those of teratomas were obvious, despite the fact that the two neoplasms could coexist in the same testis, sometimes apart and sometimes intermingled. The gross and microscopic appearance of the seminoma, its sensitivity to irradiation and its good prognosis were also readily recognized. The specialized lymphoid or granulomatous stroma, which characterizes seminomas in any location, has led to the speculation that it might represent an immunologic reaction,[7] possibly a host-graft response. The granulomatous tissue rarely replaces the seminomatous so completely as to be misdiagnosed as granulomatous orchitis.[1]

Seminomatous cells are often present as individual elements within the surviving normal tubules at the margins of all types of germinal tumors. They represent the residua of the earliest stage in the development of the tumors and not a secondary invasion.

The spermatocytic seminoma,[8,9] which should be regarded as a specialized subtype, actually differentiates into homologues of the seminiferous epithelium; by contrast, the cells of the classical seminoma are homologous with primordial germ cells. The spermatocytoma is restricted to the postpuberal testis, whereas the seminoma can also occur in the ovary, thymus and pineal. Although the latter is associated with the usual array of teratoid tumors, the spermatocytoma is not. It represents differentiation toward the gamete, whereas the seminoma is totipotential.

Mostofi[4] considers anaplastic seminoma to be another subtype of the classical seminoma. The foci of embryonal carcinoma (which may be seen within seminomatous tissue[10] and within the transition zone in the occasional tumor combining seminoma and embryonal carcinoma) may signify transformation rather than classical anaplasia. There is an infrequent variant of seminoma in which giant syncytiotrophoblastic elements appear to emerge directly in the midst of purely seminomatous elements.[10-12]

With regard to trophoblast, it must be reemphasized that the "villi" in testicular choriocarcinoma are pseudovilli and lack the stromal and vascular cores of "true" chorionic villi.[10,13] Another unusual characteristic of trophoblastic tumors is the capacity for spontaneous regression leaving, at times, only a peculiar testicular cicatrix to mark the site of origin of a tumor whose metastases may have flourished and killed the patient.[10-12]

Pathogenesis of Germ Cell Tumors

To be worthwhile, a classification of tumors must be histogenetically sound, clear to oncologists as well as pathologists, and both therapeutically and prognostically useful. By minor modification and rearrangement of Mostofi's categories,[14] and by indicating the lines of development and differentiation between the various neoplastic entities, it is possible to construct a dynamic classification of testicular germ cell tumors (Figure 1).[15] This classification is supported by an overwhelming mass of evidence from a multitude of studies dealing with both human and animal tumors, from the disciplines of experimental pathology, embryology, genetics and electron microscopy.

Primordial Germ Cells

The existence of the primordial germ cells, their pregonadal origin and their migrations are well established.[16,17] There is little doubt as to their relationship to teratoid tumors.[10,18] The re-

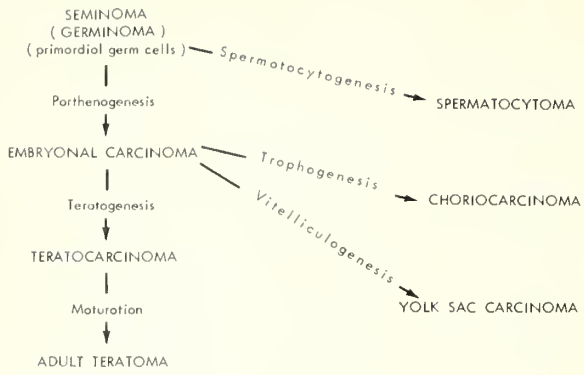

Figure 1.—Pathways of differentiation and transformation in testicular tumors. Oncogenesis recapitulates ontogenesis.[15]

semblance of seminoma cells to primordial germ cells in the normal human embryo is striking.[19] A high content of both alkaline phosphatase and glycogen, although not specific, is nevertheless common to both the cells of seminomas and to primordial germ cells.

Experimental interference with the extragonadal primordial germ cells results in a testis deficient in germ cells.[20-22] Genetic faults in C57 black mice homozygous at the W locus result not only in germ cell faults but also in anemia and pigmentary disturbances.[21,23] Stevens[24] showed that mice homozygotic for a comparable gene defect, and whose gonads had very few primordial germ cells, yielded only a 3 percent teratoma harvest as against 75 percent for the control mice whose gonads had normal numbers of primordial elements.

Metastases

The altered histologic patterns in metastases as compared with the morphologic pictures of the primary tumors are best explained in terms of progressive, metachronous or dissociated differentiation.[1,3,4]

Ovarian Tumors

Meyer,[25] recognizing the identity of the ovarian dysgerminoma with testicular seminoma, attributed the origin of both to a primitive cell before the stage of sexual differentiation. All of the teratoid types seen in the testis are encountered in the ovary, with the exception of the spermatocytic variant.[2] Another significant variation is the pronounced degree of differentiation seen in the ovarian teratomas as opposed to the less advanced level of tissue complexity attained by the testicular homologues.[1,11]

Extragonadal Tumors

Tumors of the pineal and diencephalon, as well as of the mediastinum and thymus, also manifest as seminomas, embryonal carcinomas, teratomas, choriocarcinomas and mixtures thereof.[11,26,27] Special subtypes, such as Teilum's yolk sac tumor, and the special stromal reactions, such as the pseudosarcoid granulomas, also occur,[7] but no spermatocytic seminomas are seen.

Experimental Teratoma Testis

The production of teratoid tumors in the intra-abdominal testes of roosters by injection of metallic salts has been successfully repeated many times.[28] The tumors begin as intratubular monocellular proliferation of embryonal elements at the edge of the testicular necrosis produced by the caustic metallic compounds. All stages from embryonal carcinoma to teratocarcinoma to teratoma can be observed.

Spontaneous Tumors in Animals

Teratomas appear in the testes of certain strains of mice; they begin as tiny intratubular cell complexes and culminate as teratocarcinomas, teratomas, choriocarcinomas and yolk sac tumors, which arise from embryonal carcinomas as in man.[29] It has even been possible to produce end-stage tumors by cloning single cells; the differentiation of teratomas from embryoid bodies can be readily observed by growing the tumor in the ascitic form.[10]

Ultrastructural Studies

Seminomas consist of a spectrum of cells including undifferentiated stem cells resembling primordial germ cells, spermatogonia, spermatocytes and embryonal carcinomatous elements, as well as elements reflecting abortive differentiation toward sperm cells.[9,10] Carcinogenesis involving the primordial cells or spermatogonia, present in prepubertal boys, could give rise to embryonal carcinoma and the teratoid series of tumors, but not to spermatocytic seminoma. In adults, where the complete series of stem cells is present, carcinogenesis could occasionally result in both the spermatocytoma and the teratoid series.

Genetic Studies

Linder, McCaw and Hecht[30] have found that ovarian teratomas are of germinal origin. By culturing cells from such tumors and studying chromosomal and enzymatic patterns, they showed

that the cell of origin must be a germ cell after the first meiotic division. In the case of the extragenital teratoid tumors they showed that the cell of origin is a nonmeiotic element, either a somatic cell or a misplaced germ cell.[31] Studies of sex chromatin[32,33] and karyotypes of teratoid neoplasms have shown "female" patterns in regular proportions of testicular growths. These data are compatible with both germ cell origin and a common ancestral element for seminomas and teratomas.[34]

Thus, the evidence from embryologic studies of the primordial germ cells, the patterns of metastasis, the homologous ovarian and extragonadal tumors, and spontaneous and experimentally induced or altered teratoid tumors in animals, as well as from ultrastructural studies and modern genetic studies, indicates that the various types of germ cell tumors are interrelated along the lines of normal embryogenesis (Figure 1).

Epidemiology

Incidence

STEPHEN A. SACKS, MD:* Tumors of the testicle approximate 1 to 2 percent of all male-related malignant neoplasms and account for 4 to 10 percent of genitourinary malignancies in men.[5,35] Testicular tumors make up the second most frequent malignant disease occurring in men between the ages of 20 and 34.[14]

Frequency and Geographic Distribution

The incidence of testicular tumors varies slightly among geographic areas in the United States, approximating 2 to 3 per 100,000 men per year.[14] This occurrence correlates well with the frequency reported from Canada, England and Wales,[14,35] but is significantly less than the occurrence reported from Denmark—that is, 4 to 6 per 100,000 men per year.[36]

Age Distribution

Testicular neoplasms have been recognized at all ages from the newborn through the ninth decade of life.[5] The peak incidence, however, occurs between ages 20 and 40.[5] Seminomas appear to develop later than other histologic types, with the average age of occurrence reported to be between 30 and 42 years. Embryonal carcinomas and teratocarcinomas tend to occur about five years earlier, and choriocarcinomas about ten years earlier, than seminomas.[5]

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Racial Differences

Significantly fewer germ cell tumors of the testicles occur in nonwhite than in white populations.[37] The incidence in blacks is a sixth to a tenth that of the white population. The greatest discrepancy in this occurrence appears in the younger age groups. These dramatic racial differences occur regardless of geographic locale and have been substantiated in American, European, Jamaican and African blacks.[37]

Such data tend to negate theories based upon latitude and mean annual temperatures as a basis for racial difference.[35] The incidence of testis tumors has also been noted to be significantly lower among Asian and Japanese.[4] It would be of critical epidemiological importance to determine the incidence of testicular tumors in nonwhite men with and without incomplete testicular descent.

Testicular Maldescent

The relationship between incomplete testicular descent and the subsequent development of germ cell tumors has long been recognized.[38] Some 4 to 12 percent of testicular neoplasms have been reported to occur in association with incomplete testicular descent, and the probability of malignant degeneration of a cryptorchid testicle is approximately 20 to 40 times greater than a normally descended testicle.[39] This relationship is not apparent in the development of testicular tumors in children.[40]

Malignant degeneration of the testicle may occur five to six times more frequently in abdominal maldescent than in inguinal maldescent,[41] and for a variety of reasons, the death rate related to malignant degeneration in the abdominal testicle appears to assume this same increase.[42] The observations that the risk of death from malignant degeneration exceeds the risk of anesthesia[43] or orchiectomy substantiates the rationale for removing the incompletely descended testicle after puberty. The development of testicular tumors in children in whom orchiopexy has been done after the age of six, but before the age of ten, is well-documented.[39,42] However, the role of hormonal or surgical orchiopexy before the age of six for the prevention of testicular malignancy has not been established.

Approximately 20 percent of cryptorchid-associated malignancy involves the contralateral, descended testicle.[39] This observation seems to support the theories of testicular dysgenesis as an

etiologic predeterminant of germinal neoplasms.[44] Finally, the ratio of right-sided to left-sided cryptorchidism and right-sided to left-sided neoplasm is approximately 5 to 4.[5] There is no satisfactory explanation for this phenomenon.

The Dysgenetic Testicle

The "dysgenetic" testicle, encountered most frequently in those maladies which we have termed "intersex," provides many clues regarding the cause of testicular tumorogenesis, but unfortunately no answers. One of the most curious of these disorders is the syndrome of testicular feminization, in which the gonad is a testicle, the karyotype is XY, but the phenotype is female. The testis is usually located in an inguinal hernia sac, and in 25 percent of the reported cases of patients over the age of 30 there were malignant germ cell tumors in these dysgenetic testicles.[45]

Bilateral Tumors

The synchronous and asynchronous occurrence of bilateral germ cell tumors has been clearly documented to exceed the limits of probability. It has been estimated that after the removal of one malignant testicle the chance of malignant degeneration in the remaining testicle is 700 times greater than for the general population. Almost all combinations of histological pattern have been reported.[46]

Familial Incidence

Numerous reports of the familial coincidence of germinal tumors of the testicle have shown that it occurs in monozygotic and dizygotic twins (with and without mirror-imaging), nontwin brothers (four in one report) and fathers and sons.[47-50] Synchronous occurrence is very rare, and different histopathology is frequent.

Trauma

A history of previous testicular trauma is frequently elicited or volunteered upon the diagnosis of a testicular tumor.[51] This relationship has been observed in approximately 8 to 25 percent of the cases reported. In addition to direct injury, there is often a history of mumps orchitis and atrophy, and occasionally a history suggestive of intermittent torsion.[52] No direct causal relationship has been established, however, between testicular trauma and the development of testicular tumors, and the prognosis is apparently not affected.[35]

Clinical Presentation

In 1779 Percival Pott made an extraordinarily perceptive assessment of the clinical presentation of tumors of the testicle: "Sometimes the first appearance is a mere simple enlargement and induration of the body of the testicle, void of pain, without inequality of surface, and producing no uneasiness nor inconvenience, except what is occasioned by its mere weight. And some few people are so fortunate to have it remain in this state for a considerable length of time, without visible or material alteration."[35] This is the clinical pattern regularly seen in modern urological practice,[52] and the "considerable length of time" alluded to by Pott between the first recognition of symptoms and the first examination by a physician usually exceeds five months.[51] Less frequently, there may be a rather sudden enlargement of a preexisting testicular mass, rapid enlargement associated with the signs and symptoms of inflammation, hemorrhage or infarction in a previously "normal" testicle.

Clinical presentation may be so subtle as to obscure an accurate initial diagnosis in 25 percent of patients. The onset of acute abdominal pain in a patient with a unilaterally descended testicle and a vacant contralateral inguinal canal should alert a physician to the possibility of torsion, hemorrhage, infarction or rupture of an intra-abdominal testicle. This clinical condition was first recognized in 1898 and is often confused with acute appendicitis.[51] Gynecomastia may be associated with testicular neoplasms but is not common as the presenting symptom. The presence of gynecomastia is usually bilateral and is not strictly correlated with any histologic pattern of disease. An evaluation of "adolescent gynecomastia" should include a thorough examination of the testicles. Approximately 10 percent of patients with testicular tumors present with symptoms referable to distant metastatic disease. These symptoms frequently include backache, skeletal pains, gastrointestinal complaints, inguinal adenopathy and neurological complaints.

Testicular tumors are often misdiagnosed as epididymitis and epididymo-orchitis. This error occurs in approximately 10 to 20 percent of patients in whom analysis is done retrospectively. If there is no funiculitis (inflammation of the spermatic cord), if the vas deferens on the involved side is not unusual and if there are no confirma-

tory signs of urinary tract infection, then tumor of the testicle must be strongly considered.

The diagnosis of simple hydrocele is made erroneously in 2 to 5 percent of testicular tumors. Frequently, a testicular tumor will have an associated hydrocele or may in itself be soft and cystic in consistency. Some authors have advocated the aspiration of a suspicious hydrocele with careful examination of the testicle immediately thereafter, although this practice could result in spread of tumor from the tunica vaginalis. Other less common differential considerations include inguinal hernia, hematoma, hematocele, torsion, spermatocele and varicocele, and rarely tuberculosis, gumma and sarcoidosis.[35,51]

When a testicular or intrascrotal mass presents a diagnostic dilemma, it is entirely advisable and appropriate to "explore" the lesion through an inguinal exposure. The spermatic cord may be readily secured at the internal inguinal ring, and the testicle with its fascial investment may be delivered intact into the area of the groin. The parietal layer of tunica vaginalis may then be opened and the diagnosis established. If the diagnosis is tumor, the testicle may be easily removed. Alternatively, if the lesion is benign the testicle may be easily returned to its hemiscrotal compartment without incurring significant morbidity. It is preferable to carry out this surgical procedure than to entertain the diagnosis of a testicular tumor and subject the patient to an unnecessarily long and uncertain follow-up.

Pretreatment Diagnostic Evaluation

RONALD W. THOMPSON, MD:* The accurate staging of patients with germ cell neoplasms of the testis requires an appreciation of the routes of dissemination, which can be local, lymphatic or hematogenous. Careful evaluation of the presenting signs and symptoms may also lend a clue to the location and size of metastasis. For example, lumbar pain may be an early sign of retroperitoneal involvement, or neck swelling and discomfort may be evidence of supraclavicular lymph node disease. Approximately 35 percent of these patients have metastasis when they are first seen, but the extent of metastasis will not be fully appreciated unless a consistent set of basic diagnostic evaluations is done.[52] The diagnostic procedures should include chest roentgenogram, intravenous pyelogram, bipedal lymphangiography, inferior venacavography (in selected cases), gonadotropin studies, and serum liver and renal function studies.

Before the advent of lymphangiography, routine studies were able to detect only 14 to 19 percent of patients with metastatic disease. With the development of this technique, Fein and Taber[53] were able to detect metastasis in 40 percent of their patients studied. Several authors have also favored testicular lymphangiography as a diagnostic procedure for evaluation of primary draining lymph nodes of the testis in the para-aortic region, which may not be opacified by foot lymphangiography.[54-56] From the practical point of view, however, by the time the patients have been referred for further diagnostic evaluation and treatment, they may have already had an orchiectomy, and the opportunity to do testicular lymphangiography is lost. Nevertheless, bipedal lymphangiography has shown an 87 percent overall accuracy in patients undergoing retroperitoneal lymph node dissection or in whom examination was done at autopsy. Despite its limitations, bipedal lymphangiography remains a viable staging tool.[52]

After these initial studies have been completed, the patient can be clinically staged. If the patient is stage A (tumor confined to the scrotum), the likelihood of additional testing showing the presence of other disease is quite low and not indicated. If there are suspicious findings, or clinical stage B (metastasis below the diaphragm) or stage C (metastasis above the diaphragm) is discovered, additional testing should be initiated. Whole lung tomography is valuable in detecting small, metastatic pulmonary nodules. Radionucleide studies are particularly helpful if symptoms indicate potential organ involvement. These include brain, bone, liver, and whole-body gallium scans. An additional procedure in stage B patients, particularly those in whom retroperitoneal node dissection is contemplated, is a biopsy of the left supraclavicular lymph node. Buck and associates[57] showed a 16 percent incidence of metastatic disease in this area in patients with stage B disease, and no evidence of metastases in patients with stage A disease.

Seminoma

Natural History

Seminomas comprise from 35 to 71 percent of primary germ cell tumors of the testes, the frequency depending on the hospital population of the series reported.[4] They occur more commonly

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in the fourth and fifth decades of life and no cases have been confirmed in infancy.[14] The right testis is more frequently involved than the left, and in about 8 percent of patients the tumor spreads beyond the capsule to the scrotal sac, the epididymis or the spermatic cord. Seminomas usually spread via the lymphatic system early in the disease and via the bloodstream later. Mostofi[14] noted that the most common metastatic sites at autopsy were the aortic and iliac nodes (71 percent), liver (54 percent), lung (57 percent), right kidney (6 percent), left kidney (37 percent), right adrenal (9 percent), left adrenal (35 percent), pancreas (21 percent), peritoneum (22 percent), pleura (17 percent) and mediastinal lymph nodes (17 percent).

Radiation Techniques

Typical seminomas have an excellent prognosis, but the overall survival rate is dependent upon the stage at initial presentation. The most significant therapeutic factor of this neoplasm is its extreme sensitivity to ionizing irradiation. If all the seminoma could be encompassed in the treatment field, as little as 1,000 rads in two weeks can eradicate this tumor in the retroperitoneal lymph nodes.[58] Most authors, however, recommend higher doses to be delivered on megavoltage units. There is a considerable range of treatment schedules in different institutions, which have all reported similar success rates in managing this disease; they have utilized 2,000 to 4,000 rads in two to four weeks, depending on the stage of disease and the extent of involvement.

In stage A disease the ipsilateral inguinal-iliac and bilateral para-aortic lymph nodes are treated to the level of the crura of the diaphragm. The hemiscrotum should be included if a scrotal incision was made, if the tunica of the testis is involved, or if residual scrotal disease is suspected. Previous surgical procedures, such as herniorrhaphy or orchiopexy with its subsequent disruption of local lymphatics, dictate whether the contralateral inguinal-iliac lymph nodes should also be treated. Doses of 2,500 rads in three weeks to 3,500 rads in 3½ weeks are given without any significant sequelae. Irradiation above the diaphragm is generally not recommended, inasmuch as the incidence of subsequent failure with this therapy is almost nonexistent.[59-61]

In stage B disease, the same areas below the diaphragm as in stage A disease are irradiated. When bulky disease is present, however, the whole abdomen should be irradiated initially because of abdominal recurrences that have subsequently been found outside the usual treatment fields.[61] Usually about 2,000 rads are delivered in three weeks with partial kidney shielding, and then the nodal areas are boosted with an additional 1,000 to 2,000 rads through much reduced treatment fields. The role of chemotherapy in reducing this bulky disease has not been systematically investigated. As this disease usually spreads by the lymphatics in the early stages, most authors[60-63] recommend prophylactic mediastinal and supraclavicular lymph node irradiation from 2,000 to 3,500 rads in two to four weeks.

TABLE 1.—*Five-Year Survival Rates of Patients with Seminomas of the Testis*

Reports	Patients* Number	Stage	Percent Survival
Doornbus et al[61]	79	A	94†
	48	B	81†
	5	C	60†
Saxena[63]	75	A & B	88
Maier et al[62]	181	A	91
	27	B	81
	11	C	18
Earle et al[60]	71	A	100
	27	B	85
	4	C	75
Ytredal and Bradfield[59]	71	A	98
	6	B	100

*All patients treated by orchiectomy and irradiation.
†Three years.

Therapy of stage C disease is determined individually. If disease is confined to lymph node structures, therapy is similar to that for stage B disease. Occasionally, if there is minimal pulmonary parenchymal disease, whole lung irradiation (1,500 rads in two weeks) with local boosts to the area of the nodule (additional 1,000 to 2,000 rads) may be successfully employed. If there is skeletal, visceral or bony disease, usually some combination of systemic chemotherapy and irradiation is recommended for maximal palliation.

Results of Therapy

Although not all authors use the same staging system, there are enough similarities to compare the results of therapy from various centers (Table 1).[59-62] In stage A, patients surviving five years vary from 91 to 100 percent. Stage B likewise has an excellent prognosis, with 81 to 100 percent of patients surviving five years. In the series of case studies (from the Armed Forces Institute of Pathology) by Nefzger and Mostofi,[64] 316 pa-

tients with all stages of seminoma were followed to 17 years after initial treatment; the survival rate in this series was 75 percent. These excellent results have been achieved in many institutions, with minimal morbidity from treatment.

Disseminated Disease

Because most patients with seminoma present in early stages A or B, and because the treatment with orchiectomy and irradiation is so successful (Table 1), the experience with advanced stage C disease or disseminated disease is limited. Seminomas, however, have shown sensitivity primarily to alkylating agents.[65] Combination chemotherapy programs have also been used with substantial objective regression rates.[66-68] Chemotherapy for bulky tumors or for advanced stage C patients, as part of the initial treatment plan rather than after a relapse, has not been explored but is to be encouraged. The five-year survival rate of stage C patients is as low as 18 percent and, obviously, calls for improvement.

Nonseminoma Germ Cell Tumors: Treatment and Prognosis

DONALD G. SKINNER, MD:* Treatment of nonseminomatous germ cell tumors of the testis remains controversial, despite recent literature reports of survival rates between 75 and 85 percent.[69-72] These improved statistics stem in part from meticulous lymph node dissection and judicious use of adjuvant modalities, including chemotherapy and radiation therapy.

Nevertheless, confusion exists regarding a rational approach to management, and some oncologists continue to believe that patients afflicted with these tumors are best managed by one modality, primarily radiation therapy.[73,74] Much of the difficulty stems from the following factors:

- The classification of nonseminomatous germinal tumors of the testis is not uniform nor is it understood, which makes it impossible to compare the results reported by various authors. Adoption of the Friedman and Moore[1] classification, based on biological behavior, greatly simplifies this problem; in a discussion of treatment, clinicians may therefore concern themselves with the overall management of the nonseminomatous group that includes all mixed forms. (Pure choriocarcinoma is an extremely rare tumor and will not be discussed in this presentation.)

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TABLE 2.—*Criteria for Pathologic Staging of Nonseminomatous Testis Tumors*

Stage	*Description*
A	Tumor confined to the scrotum. X-ray film of chest and intravenous pyelogram negative. No positive nodes on lymph node dissection.
B	Tumor metastases present below the diaphragm. X-ray film of chest and mediastinum normal.
B_1	Gross or microscopic involvement of fewer than six well-encapsulated nodes, with no evidence of tumor extending through the node capsule and involving the retroperitoneal fat.
B_2	Gross or microscopic involvement of more than six nodes, or tumor extending through the node capsule and involving the retroperitoneal fat.
C	Metastases present above the diaphragm.

- Inasmuch as patients with testis tumors are not numerous, it is difficult to develop a plan of management. There is, therefore, a tendency for one therapeutic modality to predominate, with not enough consideration given to a combined approach.
- It has only recently been shown that lymph node dissection can effectively remove the retroperitoneal nodes,[75] but indiscriminate use of postoperative radiation therapy in most surgical series has made it difficult to evaluate the contribution of lymphadenectomy to improved survival.
- Accurate staging is difficult unless surgical lymphadenectomy is done; moreover, many reports exclude advanced cases, thereby making biased patient selection an important factor in survival statistics.

We have recently reported[69] the results of treating 96 consecutive patients, with no exclusions, including 17 with stage C disease. Experience with these patients has led to a plan of management based on retroperitoneal lymph node dissection as the primary treatment modality, with use of adjuvant therapy as determined by the pathologic stage. Criteria for pathologic staging are listed in Table 2.

Patients who present with pulmonary metastases (stage C) or with clinical evidence of massive retroperitoneal disease are initially treated by a course of intensive inpatient chemotherapy (Table 3),[69] followed three weeks later by a five-week outpatient course of bleomycin (30 units given intramuscularly twice a week for five weeks, 300 units total) and vinblastine sulfate (10 mg given intravenously on day 1; 15 mg given intravenously on day 8, 20 mg given intravenously on day 21). After three weeks, retroperitoneal

TABLE 3.—*Initial Inpatient Course of Chemotherapy Given to Patients with Disseminated Disease (Stage C) or Clinical Evidence of Massive Retroperitoneal Disease*

Day	*Drug*	*Dosage*
1 ..	Actinomycin D	1.0 mg i.v. over 3 hr
	Cyclophosphomide (Cytoxan®)	2.0 mg/kg body weight i.v.
	Methotrexate	5.0 mg i.v.
2 ..	Repeat actinomycin D	
	Repeat Cytoxan	
3 ..	Repeat actinomycin D	
	Repeat Cytoxan	
	Repeat methotrexate	
4 ..	Repeat actinomycin D	
	Repeat Cytoxan	
	Vincristine	2.0 mg i.v.
	Prednisolone	20.0 mg p.o.*
5 ..	Repeat actinomycin D	
	Repeat Cytoxan	
	Repeat methotrexate	
	Repeat prednisolone	
6 ..	Actinomycin D	0.5 mg i.v.
	Repeat prednisolone	

*Prednisolone given to reduce toxicity.

TABLE 4.—*Survival for All Patients According to Pathologic Stage**

Stage	*Number*	*Survival Percentage*
A	39/43	91
B_1	12/14†	86
B_2	16/22	73
	67/79	85
C	8/17‡	47
Total	75/96	78

*From Skinner.[69]
†One death: operative mortality.
‡One postoperative suicide (18 months); no evidence of tumor at autopsy.

TABLE 5.—*Survival According to Cell Type**

Cell Type	*Survival*	
	Number	*Percentage*
Embryonal	28/36	78
Mixed	9/13	69
Teratocarcinoma	46/57†	81
Mixed	12/16	75
Choriocarcinoma	1/2	
Chorio Elements	10/14	71
Seminoma Elements	13/17	77

*From Skinner.[69]
†One operative mortality excluded.

lymph node dissection is done to remove bulk disease.

The retroperitoneal lymph node dissection is usually accomplished through the thoracoabdominal approach, which allows wedge resection of ipsilateral pulmonary metastases, a careful evaluation of the mediastinum and complete removal of all retroperitoneal metastatic disease. Dissection was done in all patients in this series, even for extensive tumor, and this occasionally included removal of the vena cava or an ipsilateral kidney.

Chemotherapy is considered the primary adjuvant, with actinomycin D as the basic drug. Dosage is based on the patient's weight and is given intravenously once a day for five days (each treatment course) (weight greater than 160 pounds: 5 mg over five days; 120 to 160 pounds: 4 mg over five days; less than 120 pounds: 3 mg over five days). Early in our investigations, chemotherapy was not generally used for patients in whom nodes were negative, but now it is our policy to initiate a course of actinomycin D during operation, continue it during the immediate postoperative period, and then repeat it once prophylactically.

In patients with pathologic stage B_1 or greater, cyclic chemotherapy with actinomycin D is recommended every two months for the first year and every three months for the second year.

If the primary tumor contains foci of choriocarcinoma, if choriocarcinomatous elements are present in metastases or if the patient has extensive retroperitoneal disease (stage B_2), at least one course of the combined vinblastine sulfate and bleomycin is substituted for the usual course of actinomycin D, given two to three months after lymphadenectomy.

Postoperative radiation therapy is reserved for those patients in whom there is extensive retroperitoneal disease (stage B_2). Beginning four to six weeks after lymph node dissection and postoperative chemotherapy, 4,500 rads are delivered to the retroperitoneum and ipsilateral iliac region. Four to six weeks after completion of radiation therapy, chemotherapy is resumed on a cyclic basis every two months for the first year and every three months for the second year.

In most patients with stage C disease, wedge resection of pulmonary metastases is done either at the time of lymph node dissection or through a formal thoracotomy three to six months after lymph node dissection. These patients receive a second full course of vinblastine sulfate and bleomycin after they have been rendered tumor-free by surgical operation; cyclic chemotherapy is continued with actinomycin D for a full two years after the last surgical procedure.

Survival for all patients in this series was 78 percent (Table 4).[69] For patients in whom disease was confined below the diaphragm, survival

was 85 percent. There was one postoperative death, representing a mortality of 1.3 percent. Table 5 lists survival according to cell type and supports our contention that the specific cell type or combination makes little difference in the total management plan or results of treatment.

Stage relates directly to the tumor-free interval and proves to be significant for survival; in no patient has there been a recurrence more than two years after lymphadenectomy. In stage A patients, the average time of tumor recurrence was 12 months, and there was no recurrence later than 22 months after lymphadenectomy. In stage B patients, average time of tumor recurrence was six months, with no recurrence later than 12 months postlymphadenectomy. In stage C patients, the average time of recurrence was three months, with a range of zero to nine months for recurrence. In no patient in stage C who was free of tumor for longer than nine months after lymphadenectomy and wedge resection of pulmonary metastases or thoracotomy was there a recurrence and none died of disease.

Within each stage, chemotherapy improved survival, and combined therapy that included radiation, surgical operation and chemotherapy resulted in notably improved survival for patients with advanced disease (Table 6).[69]

When surgical therapy fails, it is nearly always secondary to disseminated disease and the development of pulmonary metastases. In only one patient in our series with stage A or B disease did retroperitoneal recurrence develop; all other failures were due to pulmonary or disseminated disease. Based on this fact, it seems prudent to combine a systemic agent with known cytotoxicity against nonseminomatous tumors with hopes of sterilizing possible microscopic foci present beyond the field of surgical resection. Various cytotoxic drugs, in addition to actinomycin D, have been used as single agents or in combination, including methotrexate, chlorambucil, mithramycin, cyclophosphamide, adriamycin, vincristine and diaminodichloroplatinum; however, actinomycin D remains the primary drug that seems most effective against the nonseminomatous group of testis tumors.[76-82]

Our experience with the combination of vinblastine sulfate and bleomycin, supported by published reports by Samuels,[83] and Samuels, Holoye and Johnson,[84] leads us to believe that this combination is extremely active against this group of tumors; we recommend its use in all patients with extensive lesions or evidence of choriocarcinoma in the primary or metastatic tumor. However, because there is a limitation to the total cumulative dose of bleomycin, long-term therapy requires resumption of cyclic actinomycin D therapy.

Early in our studies, prophylactic chemotherapy was seldom used for patients with stage A or B_1 disease, but results indicated that in 18 percent of these patients pulmonary metastases developed and that they subsequently died of the disease. In other surgical series, the results are similar, regardless of whether postoperative radiation therapy to the retroperitoneum was employed. When failure occurs, it is almost always secondary to pulmonary metastases. Staubitz and colleagues[71] reported that pulmonary metastases developed in six of their 45 patients (13 percent) in whom nodes were negative. Consequently, it is our current practice to treat all stage A patients prophylactically with two courses of actinomycin D therapy; if elements of choriocarcinoma are present in the primary tumor, cyclic chemotherapy is continued for two years, in addition to one course of vinblastine sulfate and bleomycin. Whitmore[72] also supports this philosophy, and our current results indicate that survival can be improved from 82 to 93 percent for patients with minimal dis-

TABLE 6.—*Survival According to Adjuvant Therapy**

	Stages					
	A-B₁		*B₂*		*C*	
Adjuvant Therapy	*Number*	*Percent*	*Number*	*Percent*	*Number*	*Percent*
None	18/22	82	1/1	100	1/1	100
Chemotherapy	28/30†	93	3/4	75	3/9	33
Radiation therapy	4/4	100	3/7	43	0/2	0
Chemotherapy + radiation	1/1	100	9/10	90	4/5‡	80
Totals	51/57	89	16/22	73	8/17	47

*From Skinner.[69]
†One death: operative mortality.
‡One patient committed suicide 18 months postoperatively; no tumor present at autopsy.

ease (stage A and B_1) treated in this manner (Table 5).[69]

We have shown that five-year survival now exceeds 90 percent for patients with negative nodes or minimal retroperitoneal metastases treated by lymph node dissection and chemotherapy. In this group, postoperative radiation therapy to the retroperitoneal area offers negligible tumor control, and resultant bone marrow toxicity further decreases patient tolerance to chemotherapy with effective cytotoxic drugs.

On the other hand, radiation therapy has been a helpful adjuvant in salvaging patients with advanced retroperitoneal metastases. It seems most effective in sterilizing microscopic residual tumors that undoubtedly remain after surgical resection of bulky, partially necrotic retroperitoneal masses. It has, therefore, been our policy to consider chemotherapy the primary adjuvant agent and to reserve radiation therapy for those patients with extensive retroperitoneal disease treated initially by surgical dissection (stage B_2). Mediastinal radiation therapy is not given unless mediastinal lymph node metastases are proven at the time of the thoracoabdominal dissection. A retrospective review of patients treated in this manner supports this concept and shows a greater than 80 percent survival for patients with stage B_2 or C disease treated with a combination of all three modalities (Table 6).[69]

Patients with stage C disease or those with clinical evidence of massive retroperitoneal disease continue to require individually tailored therapy. It is important to demonstrate a response to chemotherapy and reduce tumor bulk before beginning aggressive ablative therapy. If this approach is not considered, extensive retroperitoneal disease may be unresectable at surgical exploration; cure or long-term survival depends on removal of bulk retroperitoneal disease. Our results indicate that many patients in whom disease was previously thought to be incurable can be saved by an aggressive planned approach that combines therapeutic modalities.

Tumor Markers

DR. BRAUNSTEIN: Testicular germ cell tumors have been found to secrete a variety of placental and fetal proteins that may be responsible for some of the clinical manifestations of the disorder, such as gynecomastia. These proteins may also serve as useful tumor markers for the diagnosis of the tumor, for following the effects of therapy directed toward the tumor and for the detection of recurrences.

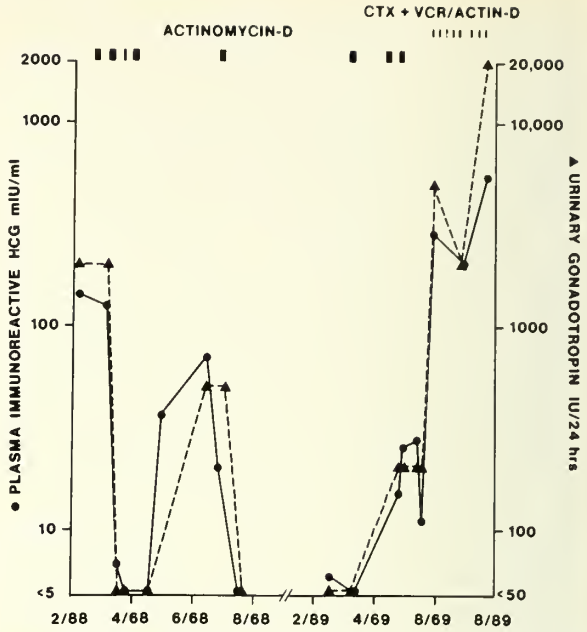

Figure 2.—Serum HCG levels measured by radioimmunoassay and total urinary gonadotropins measured by the mouse uterine weight method in a patient with metastatic teratocarcinoma of the testicle. Both the serum HCG and urinary gonadotropins paralleled the clinical course and other objective measures of remission and exacerbation.

Human Chorionic Gonadotropin

Human chorionic gonadotropin (HCG) is a glycoprotein hormone normally produced by the placental trophoblast during gestation. In 1927, Aschheim and Zondek[85] described the formation of hemorrhagic follicles in the ovaries of immature mice after injection of the urine of a pregnant woman. This bioassay was a measure of the ovarian-stimulating activity of HCG. In 1929, Zondek[86] observed a 30-year-old man with a metastatic testicular tumor whose urine produced a typical Aschheim-Zondek reaction. The patient's pituitary was free of the hormone. When tumor tissue was implanted into mice, the characteristic ovarian reaction resulted, implying that the tumor was a source of the HCG.[86] Since then, the measurement of HCG has become an essential part of evaluation in a patient with a suspected testicular tumor, and when present, this hormone has proved extremely useful for following tumor progression or regression (Figure 2). The source of the hormone appears primarily to be the trophoblastic elements in these tumors,[87] although in some HCG-secreting testicular tumors no trophoblastic elements could be identified.[88] The recent

identification of HCG (or an HCG-like substance) in the normal human testes,[89] suggests that some of the totipotential germ cells—which may be the precursors of germ-cell tumors—may have retained the capacity to secrete HCG. Neoplastic differentiation of these germ cells along nontrophoblastic lines may account for the HCG secretion by pure seminomas and embryonal-cell carcinomas.

Various methods for measuring HCG have been devised. Until recently, bioassays had been the procedure of choice. Although several biologic responses in many different species of animals have been described, the most widely used test measures the increase in the uterine weight in immature mice; the uterine enlargement is caused by the enhanced ovarian estrogen secretion that results from exposure to the HCG contained in the serum of urine of patients with trophoblastic neoplasms.[90] This procedure requires many mice, several days of injection of serum or urine in multiple dilutions, and concentration techniques when urine is the biological fluid in which HCG is measured. At low concentrations of HCG, the method is not specific, as the same biologic response may also be elicited from human pituitary luteinizing hormone, a glycoprotein with close structural similarity to HCG.

Both HCG and human luteinizing hormone are composed of two subunits, alpha and beta. The alpha subunit of these two hormones is similar, whereas the beta subunit of HCG contains 30 C-terminal aminoacid residues in excess of those present in the beta subunit of human luteinizing hormone.[91] Because of this structural similarity, radioimmunoassays, which were developed using antibodies directed against the intact human chorionic gonadotropin molecule, were unable to discriminate between HCG and luteinizing hormone. This specificity problem was resolved when a sensitive radioimmunoassay for HCG was developed that utilized an antiserum generated against the beta subunit of HCG.[92] This technique measured low levels of HCG in the presence of physiologic amounts of luteinizing hormone. Utilization of this assay has increased the detection of HCG in patients with germ cell tumors of the testes in comparison with the incidence as determined by bioassay (Table 7).[3,67,88,93-100]

The methods generally used by clinicians for measuring HCG are the commercial immunological urinary pregnancy heme-agglutination or latex-agglutination slide and tube tests. These tests have the advantages of convenience, low cost and rapidity, but *cannot* be used to exclude an HCG-secreting testicular tumor as a diagnostic consideration. Because of the above-mentioned immunologic cross-reaction between HCG and luteinizing hormone, when the intact molecules are used as immunogens, the sensitivity of these commercial tests is set at a level high enough to eliminate interference with the levels of luteinizing hormone reached during the midcycle surge of this hormone in menstruating women, or by the elevated levels found in postmenopausal women. Therefore, low levels of HCG will be missed if the urinary pregnancy tests are relied upon. Indeed, we have shown that between 33 and 44 percent of the patients with testicular tumors, in whom HCG was detected in the serum by the beta subunit radioimmunoassay, would not have had HCG detected if the commercial slide test had been solely relied upon (Table 8).

Measurement of HCG in patients with testicular tumors has been most useful in the follow-up of the effects of therapy. In many instances the HCG levels reflect the tumor burden, rising and falling in concert with other objective measurements of remission and exacerbation.[93,101] Exceptions are found, however, in patients with complex tumors consisting of different neoplastic elements (for example, teratocarcinoma) in whom the HCG

TABLE 7.—*Frequency of Human Chorionic Gonadotropin (HCG) Detection by Bioassay and Radioimmunoassay in Patients with Germ Cell Tumors of the Testes*

	Pathologic Classification							
	Seminoma		*Embryonal Carcinoma*		*Teratocarcinoma*		*Choriocarcinoma*	
Method	*Number*	*% Positive*	*Number*	*% Positive*	*Number*	*% Positive*	*Number*	*% Positive*
Bioassay*	283	19.9	154	30.5	193	32.2	39	82.1
Radioimmunoassay†								
Braunstein et al[88]	16	37.5	48	56	4	50	8	100
Cochran et al[100]	18	5.5	20	35	12	33	3	100

*Combined results of 10 series.[3,67,93-99]
†Two radioimmunoassay series listed separately because of a four-fold lower limit of detection in the method reported by Braunstein et al.[88]

TABLE 8.—*Serum Human Chorionic Gonadotropin (HCG) by Radioimmunoassay versus Expected Urinary Pregnancy Test Results in 84 Patients with Germ Cell Tumors of the Testes*

	Urinary Pregnancy Test		
Serum HCG	*% Negative*	*% Equivocal*	*% Positive*
Negative	36.9	0	0
Positive	33.3	10.7	19.1

levels may decrease despite tumor progression.[102] In these instances, radiation or chemotherapy may interfere with the synthesis of HCG by these tumors or may eliminate the HCG-secreting components, while not affecting the other neoplastic cell types. The persistence of HCG in the serum or urine of a patient with a testicular tumor is unequivocal evidence that the patient has residual disease.

The prognostic significance of the presence of HCG has been disputed. Several authors have stated that the presence of HCG in the serum or urine of a patient with a testicular neoplasm implies a poor prognosis.[94,103,104] These conclusions were based upon bioassay determination of HCG. Because of the specificity problems noted above, the levels of urinary gonadotropin had to be moderately elevated before the gonadotropin could be identified as HCG. Therefore, those patients in whom HCG is detected by bioassay may represent a group of patients with a larger tumor burden than those in whom HCG levels are undetectable by bioassay, but detectable by radioimmunoassay.

Alpha-Fetoprotein

In 1964, Tatarinov[105] described the presence of an alpha$_1$ globulin in the sera of human fetuses, in newborn infants and in patients with primary hepatomas. This protein is normally synthesized by the yolk sac, the gastrointestinal tract of the fetus, and by the fetal liver parenchymal cells.[106] Measurement of alpha-fetoprotein (AFP) has been used extensively for the diagnosis of hepatocellular carcinoma, in which elevated AFP levels are present in the blood of over 70 percent of the patients.[107] The association of AFP with testicular teratocarcinomas was reported simultaneously in 1967 by Masopust and associates[108] and Abelev and colleagues.[109] Since then, several investigators, using various methods for measuring AFP, have found elevated levels of this protein in 75 percent of the patients with teratocarcinoma or embryonal carcinoma of the testes (Table 9).[107,110-115] There was no evidence of elevated AFP in patients with pure seminomas or choriocarcinomas of the testicle. Several recent pathologic and immunofluorescence studies have shown that the cells responsible for AFP synthesis in testicular neoplasms are derivatives of the extraembryonic, primitive yolk sac.[111,116-118]

Alpha-fetoprotein is most sensitively measured by radioimmunoassay, which is also the procedure of choice for following the effects of therapy (Table 9).[107,109,115] As with HCG, the quantitative level of AFP correlates roughly with the tumor burden,[110,113,115] and changes in the level of AFP often—but not always—parallel other objective indices of changes in tumor growth.[102,115,119] As the site or origin of AFP differs from that of HCG, measurement of AFP should be part of the initial evaluation in all patients with testicular germ cell tumors (vide infra).

Carcinoembryonic Antigens

In 1965, Gold and Freedman[120] described a beta globulin that was present in colonic adenocarcinomata and fetal gastrointestinal tract. During the following ten years, many studies have elucidated the structural characteristics, heterogeneity, and normal and pathologic distribution of this substance.[121,122] Various methods of measurement have also been described.[123-125] There have been relatively few studies in which the sera of patients with testicular tumors have been exam-

TABLE 9.—*Results of Serum Alpha-Fetoprotein Measurements in Patients with Germ Cell Tumors of the Testes**

	Method†			
	Gel Diffusion		*Radioimmunoassay Radioimmunodiffusion*	
Cell Type	*Number*	*% Positive*	*Number*	*% Positive*
Seminoma	84	0	45	0
Teratocarcinoma and embryonal carcinoma	189	40.7	163	67.5
Teratocarcinoma after therapy	58	24.1	58	58.6

*Data from Waldmann and McIntire,[107] Abelev,[110] and Elgort et al.[115]
†Method sensitivities: Gel diffusion, 1-3 ug/ml; radioimmunoassay, 1 ng/ml; radioimmunodiffusion, 15 ng/ml.

ined for the presence of CEA (Table 10).[114,126,127] Although Wahren and Edsmyr[114] noted specific CEA immunofluorescent staining of a low percentage of cells in two of the four teratocarcinomas examined, the specific neoplastic element responsible for CEA production in germ cell tumors is unknown. The value of serial CEA measurements in following tumor progression or regression is currently unknown.

Other Antigens

Human placental lactogen (chorionic somatomammotropin) and placental alkaline phosphatase (Regan isoenzyme) are proteins normally synthesized by the placenta. Both have been shown to be secreted by some testicular germ cell tumors.[128-131] In the patients in whom tumors secrete placental lactogen, HCG is also produced.[129] The site of production of this material appears to be in the syncytiotrophoblastic and cytotrophoblastic elements in the tumors.[132] At present, not enough information is available regarding the value of serial measurements of these substances for evaluating tumor progression or regression.

Multiple Tumor Markers

Several groups of investigators have examined the sera of patients with testicular teratocarcinomas for the presence of more than one tumor antigen.[102,107,114,133,134] Braunstein, McIntire and Waldmann[102] described three cases of patients in whom tumors produced both HCG and AFP. Serial measurements of these proteins throughout the course of the patients' diseases showed discordant behavior of both proteins with each other. In two of the patients the HCG levels became undetectable despite persistence and growth of metastatic deposits. The AFP levels, however, remained elevated and paralleled the course of the patients' diseases. In the third patient, the AFP levels fell into the normal range, while the HCG titer correlated with progression of the tumor.

An expanded study of 101 patients with teratocarcinoma or embryonal carcinoma showed that in only 11 percent of the patients were findings negative for both HCG and AFP; in 58 percent both markers were present in sera; in 17 percent there were negative HCG levels with elevated AFP, and in 14 percent there was HCG production by the tumors with no elevation in the AFP levels.[107] Therefore, in 31 percent of the patients in this series there was elevation of only one of the two markers studied. Serial measurements of both HCG and AFP were carried out in 17 patients with disseminated disease, and discordance in the behavior of these proteins was again noted. Therefore, both HCG and AFP measurements should be made, at least initially, as part of the evaluation in a patient with testicular tumor. If levels of both proteins are elevated, then serial measurements of both of these substances should be carried out, as declining values of either one may not accurately reflect the status of the neoplastic process.[102,133]

Wahren and Edsmyr[114] measured both CEA and AFP in the sera of 32 patients with testicular teratocarcinomas. In 9 percent of the patients there were elevated levels of both CEA and AFP, in 47 percent neither antigen was elevated, in 25 percent there were elevated CEA levels with no elevation of AFP, while in 19 percent there were elevated AFP levels without a concomitant elevation of CEA.[114] Although no studies reported to date have examined serial CEA levels in patients with testicular tumors, it would seem prudent to measure this antigen as well as HCG and AFP in patients with testicular tumors.

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TABLE 10.—*Results of Serum or Plasma Carcinoembryonic Antigen Measurements in Patients with Germ Cell Tumors of the Testes*

		Pathologic Diagnosis			
		Seminoma		*Teratocarcinoma*	
Report	*Year*	*Number*	*% Positive*	*Number*	*% Positive*
Reynoso et al[126]	1972	9	44.4	12	50.0
Laurence et al[127]	1972	1	100.0	7	71.4
Wahren et al[114]	1974	23	4.4	32	34.4
Totals		33	18.2	51	43.1

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Refer to: Ischemic disease of the colon and oral contraceptives—Medical Staff Conference, University of California, San Francisco. West J Med 126:378-385, May 1977

Ischemic Disease of the Colon and Oral Contraceptives

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Associate Professor of Medicine, and H. David Watts, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, CA 94143.

DR. SCHMID:* *This morning, Medical Grand Rounds will begin with a case presentation and discussion of ischemic disease of the colon. Dr. John Cello, chief fellow in gastroenterology, will lead the discussion.*

DR. CELLO:† Recently an apparent association between atypical vascular lesions in the large bowel and oral contraceptive usage in young women has been suggested.[1-10] The spectrum of ischemic disease in the large bowel seen in these young patients has extended from colonic infarction to transient ischemic colitis which resolves without sequelae. In some patients with severe ischemic damage to the large bowel without transmural necrosis, healing results in extensive fibrosis and stricture formation. This condition presents a diagnostic problem and requires that ischemic bowel stricture be distinguished from other focal constricting lesions in the large bowel including Crohn's disease and carcinoma. We have recently seen a young woman whose case history illustrates this diagnostic problem.

*Rudi Schmid, MD, Professor of Medicine, Chief of Gastrointestinal Unit.

†John P. Cello, MD, Chief Fellow in Gastroenterology.

Case Presentation

This was the first University of California Hospital admission for a 33-year-old white woman referred for evaluation of abdominal pains and hematochezia of eight months' duration and altered bowel habits of one month's duration. Eight months previously the patient noted the onset of cramping, left lower quadrant abdominal pains, unrelated to meals, activity, position or bowel habits. One month later she noted the onset of infrequent bright red clots of blood around well-formed normal appearing stools. There was no melena, diarrhea, constipation, tenesmus or excessive mucus production.

The abdominal pains continued, still predominantly in the left lower quadrant. A sigmoidoscopy and rectal biopsy were done and findings were completely normal. Five months before admission, the pains increased in severity. The hematochezia persisted. Results of barium enema study were interpreted as being normal at that time (Figure 1). She was treated with psyllium hydrophilic colloid (Metamucil®) for "irritable bowel disease" without relief. One month before admission, the patient noted pronounced altera-

Figure 1.—Barium enema study, five months before admission. Spasm, rigidity and edema in the descending colon are clearly shown to exist by this study. This examination's findings were originally interpreted as normal.

tion in bowel habits with passage of pencil-thin, soft stools and intermittent rectal bleeding.

The patient was referred to the University of California, San Francisco, Medical Center for further evaluation. She reported that there had been no fever, chills, anorexia, nausea, vomiting, iritis, jaundice, painful skin lesions, easy bruisability, diabetes, heart disease or previous abdominal surgical procedures. The family history was negative for inflammatory bowel disease and colonic cancer. The only medication taken by the patient was norethindrone with mestranol (Ortho-Novum 1/80®) which she had been taking for a year before admission. On physical examination the patient seemed to be in no distress. No abnormalities were noted on general examination except for the presence of psoriasis. On examination of the abdomen, bowel sounds were normal and there was mild left lower quadrant tenderness on deep palpation. There was no organomegaly nor were there any masses. Results of a rectal examination were unremarkable, showing no hemorrhoids, fissures, fistulae or masses. A stool guaiac test was negative.

Laboratory studies showed the following values: hematocrit, 36 percent; red blood cell indices, normal; reticulocyte count, normal; erythrocyte sedimentation, 23 mm per hour; leukocyte count, 11,400 per cu mm with a normal differential. Findings on other tests—including a Sequential Multiple Analysis (SMA-12); serum electrolyte, prothrombin time and partial thromboplastin time determinations, and analysis of urine—were within normal limits. An x-ray film of the chest, flat plate of the abdomen and admission electrocardiogram likewise showed no abnormalities. Initial evaluation of the patient included a thorough review of radiographs taken five months before admission. Results of the earlier barium enema study (Figure 1) were reinterpreted. This time a long area in the mid-descending colon with mild narrowing and alteration of the mucosal fold pattern was identified. A repeat barium enema study (Figure 2) was done which showed a short segment of the mid-descending colon to be notably narrowed with overhanging margins, but normal appearing mucosa. The remainder of the bowel examination was without evidence of inflammatory bowel disease or malignancy. A colonoscopy was carried out. Normal mucosa was observed from the rectum to the mid-descending colon. The area of stenosis was identified and the mucosa here was edematous, friable and ulcerated. The colonoscope could not be passed through the stenotic

Figure 2.—Barium enema study on admission to the hospital. A short area of pronounced narrowing with normal mucosa, but slightly overhanging margins is well outlined by this second barium enema study using the double-contrast technique.

area. Biopsies of this region showed only acute and chronic inflammation without evidence of malignancy or granuloma. Clinically, the suspicion of malignancy was still high in view of the radiographs and colonoscopic features. The patient was taken to surgery where at laparotomy the stenotic area of the descending colon was identified and felt to be firm but not hard. There was no evidence of abdominal metastases. A left hemicolectomy was done. The mesenteric vessels were noted to pulsate normally.

On pathologic examination (Figure 3), a 3 cm ulceration with raised, irregular margins and a stenotic lumen was noted. No gross atherosclerosis or thrombosis of the large vessels was seen. Microscopic study showed acute and chronic inflammation, full thickness scarring, deep mucosal ulcerations and multiple small arterial thrombi with partial recanalization (Figure 4). There was no evidence of malignancy or granulomatous disease. Postoperative recovery was uneventful and the patient was discharged. She was advised against using oral contraceptives and was fitted with a diaphragm.

Figure 4.—Microscopic view of ulcer rim. The continuity of the colonic mucosa is lost at the beginning of the ulcer crater. Exudate consists mostly of polymorphonuclear leukocytes, while the submucosa is thickened with fibrous tissue. No malignant cells or granulomas were seen.

Discussion

A report of thromboembolic phenomena in patients taking oral contraceptives was first published by the British Family Planning Association in 1962 in the *British Medical Journal*.[3] Reed and Coon in the *New England Journal of Medicine* in 1963 provided the first American reports of thrombotic episodes in patients receiving birth control pills.[4] One of the four cases reported by them was that of a 37-year-old woman who had been taking progestational agents for only two months; acute abdominal pain developed and subsequently superior mesenteric venous thrombosis was found. This case represented the first reported incident of mesenteric vascular disease in a young woman using birth control pills. Re-

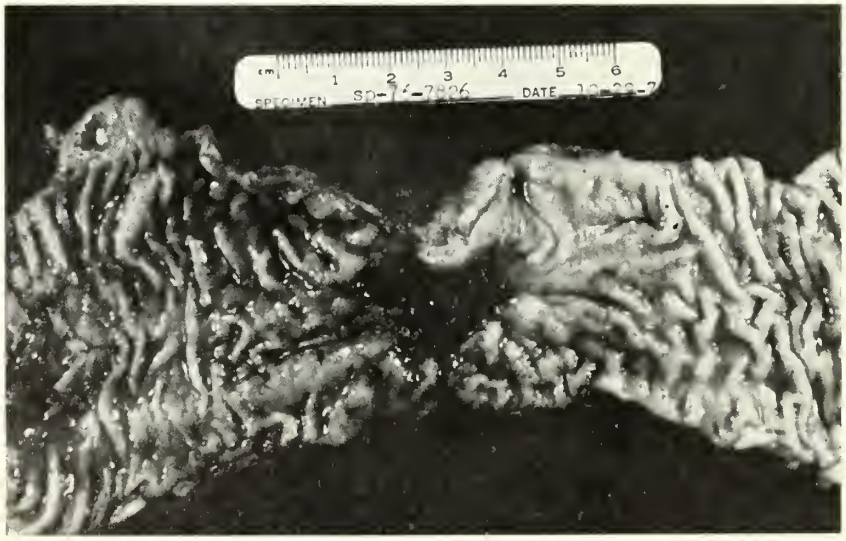

Figure 3. — Surgical pathology specimen. A discrete 3 cm ulcerative area is noted with thickening of the crater margins. The remainder of the specimen is normal. The large vessels included in the specimen were without occlusion.

cently, multiple reports have appeared of thromboembolic complications in patients taking oral contraceptives. Up to late 1976, there have been 34 cases of ischemic mesenteric vascular disease reported in women taking estrogen and progestogen medications. The age range is from 20 to 45 years. No relationship has been shown to exist between thromboemboli and the duration of oral contraceptive usage. Some patients had been taking medications for as brief a period as three to four months, while most of them had been using oral contraceptives for a number of years. There have been reports of ischemic colonic disease associated with the use of high-dose estrogen or high-dose progestogen combinations, sequential pills, or even orally or parenterally given progestogen alone.[9]

Most of the 34 women taking birth control pills in whom mesenteric vascular disease developed had the acute, sudden onset of crampy or colicky lower abdominal pains, occasionally accompanied by vomiting, but invariably accompanied by hematochezia or bloody diarrhea. In some cases, an acute condition in the abdomen has been seen. Most patients were seen early by their physicians, but some patients, such as in the present case, had waited many months before seeking medical attention. General or local abdominal tenderness without rebound usually has been found on physical examination.

A precise cause for the mesenteric vascular ischemia was defined in only a few patients, predominantly those who died or those in whom arteriographic studies were done.[4,6,8] Of those patients in whom studies were done at autopsy or by arteriography, large vessel mesenteric arterial or venous thrombosis was present in approximately 50 percent.[6] A mortality of 29 percent has been noted, largely involving those patients in whom there was extensive mesenteric vascular ischemia of both the large and small bowel.[6] There is one report in the literature of a patient in whom an episode of ischemic colitis occurred, followed four months later by the development of a stricture in the descending colon.[10] In most of the cases reported in the literature only mild symptomatology was present, the patients needed only supportive care and colonic strictures did not develop. Some patients were treated with antibiotics, steroids, low molecular weight dextran[6] and even with heparin. No controlled clinical study exists to support the use of these agents in treating this disorder.

Numerous hypotheses have been raised concerning the possible causal relationship between oral contraceptives and the increased incidence of thromboembolic complications.[10-12] In patients given progestational agents there are well documented increases in blood coagulation factors that are similar to, but in fact less than, those seen in pregnancy.[13,14] There has been no clear evidence, however, that these changes in individual coagulation factors and in the various clotting function tests define a true "hypercoagulable state" and no documentation that they can predict the occurrence of thrombosis.[12] Although many case reports have suggested that patients on a regimen of birth control pills are at an apparently increased risk of thromboembolic complications, very few prospective studies of such cases exist. In the few large prospective trials conducted, no difference could be shown in the incidence of thromboembolic phenomena in patients receiving birth control pills when carefully compared with well-matched controls.[12]

Ischemic disease of the large bowel is poorly understood, and is often misrepresented as a disease solely of the elderly with severe atherosclerotic obstructive disease of the mesenteric vessels resulting in arterial thrombosis and colonic infarction.[15] In addition, all colonic ischemic disease is erroneously assumed to be acute in presentation and catastrophic in its outcome. Results of animal experiments have suggested that ischemic disease of the colon is not simply an all-or-none phenomenon produced by the occlusion of large mesenteric vessels resulting in colonic infarction. The acute ligation of the two major colonic arteries in normal dogs produces, at most, a transient ischemic process which regresses completely in as short a time as 20 days.[16] No colonic infarction and no stricture formation occurs in experimental animals under these circumstances. These and other experimental studies as well as well-documented human case reports have necessitated a reevaluation of our concepts of colonic vascular disease.

The full spectrum of ischemic disease of the colon has been reported from multiple causes (Table 1).[16-24] Thrombosis, either arterial or venous, large or small vessel, remains among the most common known cause of ischemic damage to the colon. The cause usually is arteriosclerotic. Thrombosis of the mesenteric vessels may occur without arteriosclerosis in polycythemia, in portal hypertension and in a colonic malignancy.

TABLE 1.—*Causes of Ischemic Colitis*

Thrombosis—arterial or venous
Arteriosclerosis
Polycythemia vera
Portal hypertension
Malignancy of the bowel
Hyperviscosity syndrome
Emboli
Vasculitis
Polyarteritis nodosa
Lupus erythematosus
Giant cell arteritis (Takayasu's arteritis)
Buerger's disease
Henoch-Schonlein disease
Surgical trauma to vessels
Incarceration of the gut
Hernia
Volvulus
Intussusception
Nonocclusive ischemia
Shock—hypovolvemic or septic
Congestive heart-failure
"Spontaneous" ischemic colitis

Arterial emboli and vasculitis such as polyarteritis nodosa, lupus erythematosus, Buerger's disease, and Henoch-Schonlein's disease have been associated with ischemic damage to the colon.[17] Damage to the large blood vessels can also occur during the course of aortic or intestinal surgical procedures, in incarceration of the gut in a hernia sac, and in intestinal volvulus or intussusception. Ischemic damage to the large bowel has also been reported in nonocclusive, shock-like "low flow" states due to hypovolemia, congestive heart-failure or sepsis. Several reports have appeared of "spontaneous" ischemic colitis.

The findings of recent studies have suggested that the variable clinicopathologic presentation of large bowel ischemic disease depends upon a series of many factors. These include the rapidity of the onset of the ischemia, the length of the colon involved, the duration of the loss of blood flow, the size of the blood vessels occluded and the efficiency of the collateral circulation.[17]

Taking these multiple factors into consideration, three separate conditions have been seen following the alteration in the normal colonic blood supply.[18] First, the most severe form of ischemic disease of the colon (and that form least frequently seen) is colonic infarction. This usually occurs only with severe alterations in blood flow such as that produced by the sudden occlusion of large vessels accompanied by poor collateral circulation or a state of generalized circulatory collapse.[19] Clinically, the patient usually reports the onset of acute intense abdominal pain (usually left-sided) accompanied by hematochezia or bloody diarrhea. A toxic condition invariably is present and the abdomen is very tender with guarding and rebound. The clinical features can be confused with those of diverticulitis, volvulus, toxic megacolon or perforated bowel. An extremely high mortality is associated with this condition.

Second, in transient ischemic colitis—by far the most common form of ischemic disease of the colon—the ischemic damage is confined almost exclusively to the mucosa and submucosa.[18] In slowly progressive, large vessel, occlusive disease the collateral blood supply develops rapidly in patients with excellent circulatory state to prevent transmural infarction. The ischemic damage is usually confined solely to the mucosa and submucosa, that portion of the bowel wall furthest away from the blood supply. In small vessel emboli and vasculitis where the larger vessels are not involved and the collateral circulation is good, ischemic damage is also restricted almost exclusively to the most superficial layers of the bowel wall. Clinically, these patients are usually middle aged with some evidence of peripheral vascular disease. They present with indolent, moderate pain of several days duration. The abdomen on physical examination is found to be moderately tender to palpation. There may or may not be gross hematochezia, but on chemical testing of the stool there will invariably be occult blood. Complete resolution is common. In most patients this condition probably goes undetected and few of them seek medical attention.

A third set of conditions may exist wherein the extent of the ischemic insult to the large bowel is sufficient to produce severe damage to the underlying muscularis propria of the bowel wall in addition to mucosal and submucosal necrosis.[17,19,23] Presumably, the ischemic episode is severe, but whether because the vessel occluded is only a segmental vessel or the patient's overall cardiovascular status is good, blood flow is restored sufficiently soon to prevent gangrenous infarction. In this condition, the patient usually presents clinically with protracted bouts of severe pain associated with hematochezia. The abdomen on physical examination is often moderately tender with some guarding and rebound. Either gross blood or occult blood will be found in stool specimens on chemical testing. In a large number of

these patients extensive fibrosis will develop in the areas of healing ischemic necrosis in the submucosal and muscular layers of the bowel wall. Stricture formation is common, as in the case presented today.

Proctosigmoidoscopic examination is occasionally helpful in these patients and findings may distinguish this entity from other forms of large bowel disease. In ischemic bowel disease, the rectum, because of its extensive collateral circulation, is rarely involved.[19] When the proximal rectum is involved, there may be edematous, hyperemic, friable mucosa—often sharply demarcated from the more normal looking rectal mucosa distally. By contrast, the rectum is universally involved in ulcerative colitis. No deep linear ulcerations of the rectum are seen in colonic ischemia, such as those found in Crohn's disease of the large bowel.

Ischemic disease of the large bowel is protean in its manifestations and must be kept in mind when any patient, young or old, presents with cramping abdominal pains and hematochezia (or in whom chemical testing of stool specimens gives positive findings). Radiography provides invaluable diagnostic aid in such patients. In patients with ischemic necrosis of the bowel, the severity of the clinical presentation precludes barium enema examination. Some help may come from careful observation of plain films of the abdomen. In those patients without an acute condition of the abdomen in whom a barium enema study may safely be done specific radiologic findings may help considerably in clarifying the diagnosis. I have asked Dr. Thoeni from the Department of Radiology to review the pattern of radiographic findings in ischemic disease of the large bowel.

Figure 5.—Thumbprinting **(arrows)** is clearly shown by the barium enema in the ascending colon. The impressions on the barium column in the colon are caused by submucosal hemorrhage and edema.

Radiographic Diagnosis

DR. THOENI:* The classic radiographic findings in ischemic colitis are thumbprinting, picket-fence thickening of the folds, sacculation, tubular narrowing and stricture. "Picket-fence thickening" refers to the appearance of the mucosal folds which are enlarged and slightly blunted in a regular pattern. This can also be seen in regional enteritis and it can be impossible to make the correct diagnosis radiographically without additional observations. Thumbprinting consists of multiple impressions on the air or barium column in the colon or ileum (Figure 5). This can take the appearance of multiple polypoid defects if seen on end. The phenomenon of thumbprinting is due to submucosal hemorrhage and edema. Interpretation of the radiographs may be difficult because intramural bleeding due to anticoagulant therapy, coagulation defects or trauma can be similar in appearance to hemorrhage and edema from vascular disease of the bowel. The "stack of coins" appearance of the folds, the absence of spasm and rigidity, the complete resolution of radiographically-observable abnormalities and, most important, the presence of a mesenteric mass are typical of intramural hemorrhage.[25] The distinction is especially difficult to make in patients who have received anticoagulant therapy because

*Ruedi F. Thoeni, MD, Instructor in Radiology.

a mesenteric vascular occlusion can occur even in these patients. Although superficial mucosal ulcerations are seen during endoscopy in areas where the mucosa is sloughed (usually overlying zones of intense submucosal hemorrhage and edema), they often cannot be observed radiographically. If they are very diffuse, the mucosal fold pattern is effaced, but when they are deep, they may be indistinguishable from those seen in primary inflammatory bowel disease. A case in which deep ulcerations were present has been described in colitis related to contraceptive drugs.[26]

If the ischemic process progresses to fibrosis, outpocketings known as pseudodiverticula or sacculations can be identified on the antimesenteric border of the large bowel. These are caused by scarring in which one side of the bowel wall, the mesenteric border, becomes rigid and flat and the opposite side plicates. If the fibrosis continues, the involved area will taper smoothly into a stricture with a concentric lumen. In general, the stricture extends over a smaller segment of bowel than the original acute changes. It is more common that a long segment is strictured, but a short stenosis is possible. Occasionally the area proximal to the stricture may become dilated.

Radiographs of the abdomen taken in the very early stages of the disease may be completely normal but paralytic ileus, enlarged haustra and thickened bowel wall can occasionally be seen (Figure 6). If the ischemia continues, pronounced distention of a segment of the bowel and in rare instances perforation can occur producing free air or pneumatosis coli (Figure 7).[27] Toxic megacolon, similar to that observed in ulcerative colitis has been reported.[28] When colonic infarction occurs, pronounced distention of the involved area, blunting of the folds and pneumatosis coli can be observed. With extensive necrosis, air lodged in the portal venous system may also be noted.

Transient ischemic colitis may show all of the classic signs mentioned above and finally terminate with fibrosis and stricture or alternatively resolve completely, depending on the clinical conditions. The change from early edema and spasm to fibrosis and stricture formation can be very rapid and strictures have been observed radiographically as soon as two weeks after the onset of the ischemic episode, but usually require four to six weeks to develop. The entire process may terminate at any stage and complete or partial healing may ensue.

The radiographic differential diagnosis of ischemic colitis should include granulomatous colitis, radiation colitis, infectious colitis and carcinoma. Skin lesions, fistulae and longitudinal

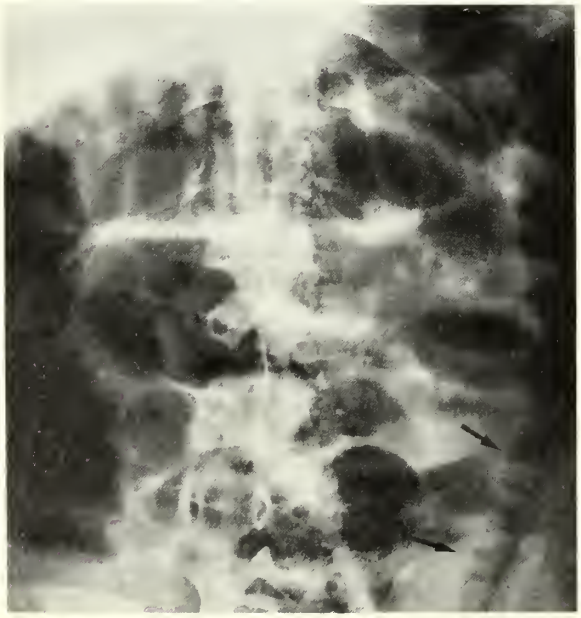

Figure 6.—Plain film of the abdomen. Thickened bowel wall and thumbprinting are evident **(arrows).**

Figure 7.—Plain film of the abdomen. On this film air in the wall of the cecum is present represented as radiolucent lines **(arrows).**

ulcerations favor a diagnosis of Crohn's disease but would be very unusual in ischemic colitis. At a very early stage, however, it may be impossible to distinguish the two entities radiographically. Colitis due to radiation, enteric infections such as shigellosis, amebiasis, and salmonellosis and ulcerative colitis also should be considered. Radiation colitis is confined to the segments of bowel which were in the radiation port, and the clinical history helps to reach the correct interpretation. Infectious disease of the colon and ulcerative colitis, though similar to an acute ischemic episode in distribution, will have small mucosal ulcerations in radiographs. Such ulcerations are very rarely observable on barium enema studies in patients with vascular disease of the colon.

Overhanging margins, destruction of the mucosa and ulcerations strongly suggest carcinoma. These features are unusual in a stricture caused by ischemic colitis which more commonly is characterized by smoothly tapered margins and a concentric lumen. In most cases, the clinical history and recent radiographs which had not shown any constricted area will be very helpful in correctly interpreting the abnormalities. Ischemic colitis may occur proximal to carcinoma.[29,30] The exact mechanisms are not known, but experimental data seem to suggest that distention of the bowel impairs blood flow.[31]

Conclusion

A case of ischemic disease of the large bowel in a young woman taking birth control pills is presented. Although no causal relationship between birth control pills and thrombotic events, particularly colonic vascular disease, has been proved to exist, the sudden appearance of severe abdominal pains and hematochezia in a young woman taking oral contraceptives should suggest one of the forms of ischemic disease of the colon. Ischemic disease of the colon is not an all-or-none phenomenon. The disease depends upon multiple factors including the occluded vessel size, the duration of the loss of flow, the presence or absence of good collaterals, the age of the patient and the overall cardiovascular status. The end result of the altered colonic blood supply from whatever cause can vary from through-and-through transmural gangrenous infarction to a very transient mucosal and submucosal inflammatory, ulcerative process that can heal completely. In some patients in whom there has been a moderately severe insult to the bowel wall, an altered repair state may ensue resulting in a fibrotic stricture. Ischemic disease of the large bowel can be differentiated in most cases by careful clinical proctoscopic and radiographic evaluation from inflammatory bowel disease and colonic malignancy.

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Important Advances in Clinical Medicine

Epitomes of Progress — General Surgery

The Scientific Board of the California Medical Association presents the following inventory of items of progress in general surgery. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in general surgery which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on General Surgery of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, California Medical Association, 731 Market St., San Francisco, CA 94103

Gallbladder and Biliary Tract Scanning with ^{99m}Tc-PG

ORAL CHOLECYSTOGRAPHY and intravenous cholangiography generally are used to evaluate diseases of the gallbladder and biliary ductal system. However, poor intestinal absorption of oral contrast agents, as well as jaundice and derangement of liver function, may result in nonvisualization of a normal gallbladder and biliary tract. In addition, the contrast agents occasionally cause adverse reactions. These problems have stimulated a search for alternatives to cholecystography and cholangiography to avoid morbidity and to make better imaging of the biliary system possible even in the presence of jaundice. Technetium-99m-pyridoxylideneglutamate (^{99m}Tc-PG) is a new nontoxic radiopharmaceutical that is taken up by hepatocytes and rapidly excreted into the bile canaliculi which enter the gallbladder through the cystic duct. Results of studies of toxicity in mice, dogs and humans indicate a wide margin of safety for this agent. Additionally, findings in experimental studies have shown that ^{99m}Tc-PG has a rapid and consistent blood clearance and urinary excretion. The concentration of the ^{99m}Tc-PG in the bile is sufficient to allow satisfactory imaging of the biliary tree and gallbladder. Therefore this agent can be used for scanning the biliary ductal system and gallbladder.

Satisfactory images of the biliary tract can be obtained using small dosages (2 to 5 mCi) of this agent. In normal human subjects, the agent reaches the liver in 5 minutes and the common bile duct (CBD), gallbladder and duodenum in 10 to 20 minutes. The gallbladder is not visualized when the cystic duct is obstructed in patients with acute and chronic cholecystitis. In partial CBD obstruction, a distended CBD is visualized and there is delay in transit of radioactivity into the duodenum. In complete CBD obstruction, no radioactivity is seen in the biliary and gastrointestinal tract up to 24 hours after the administration of ^{99m}Tc-PG, but there is immediate and intense secretion of the radioactive agent into the genitourinary system. This is probably due to biliary stasis and lack of dynamic movement of the bile necessary for carrying the radioactive agent into the biliary ductal system down to the point of obstruction. Hepatocellular disease is characterized by delayed liver clearance and delayed visualization of the biliary and gastrointestinal tracts. In patients with asymptomatic cholelithiasis without ductal obstruction, biliary scanning is inferior to oral cholecystography for the detection of gallstones, although the gallbladder and biliary ductal system are well visualized.

The advantages of biliary scanning include safety, simplicity and availability. In addition, it

can be done in jaundiced patients as well as in those allergic to radiologic contrast agents. At present, ^{99m}Tc-PG cholescintigraphy is preferable in the initial evaluation of patients with acute cholecystitis or jaundice, while oral cholecystography is desirable in the initial evaluation of nonjaundiced patients with cholelithiasis.

NATHANIEL M. MATOLO, MD

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Surgical Management of Portal Hypertension with Variceal Hemorrhage

NEWER SURGICAL TECHNIQUES have been developed in the past decade for treating patients with portal hypertension and variceal hemorrhage. The significant metabolic impairment, notably hepatic encephalopathy and hepatic failure, that occurs following portacaval decompression led Warren to devise the selective, distal splenorenal shunt. Drapanas popularized the use of the H-graft (a prosthetic shunt) between the superior mesenteric vein and vena cava. Although the results of operations using these approaches have been encouraging, recurrent blood loss due either to shunt thrombosis or persistent portal hypertension despite a patent shunt has occurred. This complication also has occurred following the original splenorenal shunt popularized by Linton, probably because the smaller diameter splenic vein is associated with a high thrombosis rate or an inadequate sized stoma for adequate portal decompression.

During the past four years, renosplenic shunts have been used at the University of California Medical Center, San Francisco, in alternate patients in whom operative management of portal hypertension was required. The caval end of the divided left renal vein is anastomosed to the side of the splenic vein. The stoma created averages 2 to 3 cm in diameter and portal pressure has been effectively reduced in all instances. The distal end of the renal vein is oversewn and renal venous drainage occurs through adrenal and gonadal tributaries or the capsular veins. A transperitoneal route usually is used for this shunt. However, in some patients in whom multiple laparotomies or attempted shunt procedures have been carried out previously, or in whom massive ascites is present, a retroperitoneal route is used for creation of a renosplenic shunt. This is an approach that avoids excessive blood loss and reduces operative time by avoiding tedious dissection. In addition, the protein-rich ascitic fluid present in patients with massive ascites is conserved, and the intraoperative and postoperative maintenance of fluid and colloid requirements is simplified.

Experience with 38 patients in whom renosplenic shunt was carried out showed there to be fewer technical problems and metabolic derangements than have been associated with other shunts. Hepatic encephalopathy developed in only one patient.

The left renal vein appears to be an acceptable autogenous conduit for portal decompression. We believe these results justify its continued use in emergency as well as elective instances in which the control of variceal hemorrhage by reduction of portal pressure is necessary.

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Adjuvant Chemotherapy of Breast Cancer

RESULTS OF two recent studies have shown that prolonged intermittent chemotherapy after operation can decrease the early recurrence rate in patients with stage 2 breast cancer. Women in both studies had a radical mastectomy (conventional, modified or extended) and had one or more positive axillary nodes. They were then randomly assigned either to a group in which no additional therapy was given or to one in which adjuvant chemotherapy was carried out.

In the first study there was a recurrence rate of 22 percent in the control group compared with 10 percent in the group treated with 1-phenylalanine mustard (L-PAM). The differences were even greater in premenopausal women (30 percent versus 3 percent) and in those in whom four or more positive nodes were present (38 percent versus 15 percent). The average follow-up after operation was nine months.

The second study reported a recurrence rate of 18 percent in the control group compared with 4 percent in the group treated with cytoxan, methotrexate and 5-fluorouracil (CMF). Statis-

tically significant differences were seen in all groups. The average follow-up was 11 months after operation.

A recurrence rate of 3.5 percent has been noted after use of CMF and bacille Calmette Guérin (BCG), with or without an irradiated allogenic tumor cell vaccine (TCV). To date 92 patients have been treated with CMF, CMF plus BCG, or CMF, BCG and TCV. The average follow-up is 13 months after operation (1 to 30 months). In eight patients (9 percent) there was treatment failure (six recurrences and two new primaries) and three died from metastasis.

The early results from these studies are encouraging. However, several questions remain unanswered. Will the delay in recurrence increase the cure rate enough to offset the side effects, inconvenience and expense of adjuvant therapy? What are the long-term side effects of prolonged chemotherapy? These and other questions suggest that adjuvant chemotherapy is still experimental and should be carried out in carefully controlled situations where the long-term effects can be evaluated.

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Endoscopic Exploration (Choledoscopy) of the Biliary System at Operation

BECAUSE THE incidence of retained stones after biliary operation depends on a surgeon's success in removing all stones during the operation, a technique has been developed to assist surgeons to locate stones at operation.

A miniature right angled telescope was designed using the Hopkins rod-lens system. Total diameter of this instrument is 5 × 3 mm including image and light transmission as well as irrigation. The sterilized choledochoscope is introduced into the hepatic and common bile ducts at operation. This instrument allows a surgeon to see inside the bile ducts and manipulate under visual control with great precision. The lumen of the major ducts and even tertiary biliary ducts in the liver can be visualized. Small stones not seen by cholangiography can be located and removed under visual control. The first preliminary report of a multi-institutional study shows that the use of choledochoscopes decreased the number of retained stones from between 8 and 10 percent to 2.7 percent in primary choledocholithotomies.

Choledochoscopy has become an important tool in surgical procedures especially in stone disease, but it also is useful for recognizing obstruction by tumor and making biopsy under visual control possible.

GEORGE BERCI, MD

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Jejunoileal Bypass for Obesity

THIS FOCUS upon the risks of jejunoileal bypass for the treatment of massive obesity is intended to provide perspective without denying the substantial benefits of the operation.

Published operative mortality rates are in keeping with those of other major operations (3 to 6 percent), but the experience of a cross section of the medical community with this elective operation is not fully tabulated. Complications such as wound infection, hernias, intestinal obstruction, pulmonary embolus, anastomotic leak and stress bleeding are particularly difficult to remedy when they occur in morbidly obese patients.

In all patients in whom this operation is done, there are postoperative sequelae which require continuing medical follow-up. These include hepatic dysfunction, hypokalemia, hypocalcemia, anemia, chronic diarrhea, renal calculi and significant arthralgias. Reoperation is required in approximately 10 percent of the patients, either because of inadequate weight loss or because of intolerable malnutrition which may be associated with hypoproteinemia and jaundice. These sequelae are seen with varying incidence and severity; some, such as hepatic dysfunction, may be transient. In our four-year experience, the operative mortality has been 3 percent. There have been few complications and almost all patients continue to express satisfaction. However, at the end of the first postoperative year, only half our patients are free of significantly adverse sequelae from a physician's viewpoint.

It is currently not clear that the significant benefits of jejunoileal bypass for obesity outweigh the substantial risks. A new complication of "colonic

pseudo-obstruction" is being recognized increasingly. The operation should be offered by interdisciplinary teams of surgeons and physicians committed to critical review of results and long-term intensive follow-up.

JOHN R. BENFIELD, MD

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Prevention of Venous Thromboembolism

VENOUS THROMBOEMBOLISM is an important cause of morbidity and mortality among patients in hospital. That 70 to 80 percent of patients who die of massive pulmonary embolism do so within two hours of the onset of symptoms emphasizes the importance of prevention. Recent large scale studies using radioactive fibrinogen to identify deep leg vein thrombosis (DVT) have shown the magnitude of the problem, identified high risk groups and proven the efficacy of prophylactic measures. At high risk for the development of DVT are patients over 40 years old in whom any operation is done that will keep them in bed for more than two to three days; patients with leg trauma (especially elderly patients with fractured femoral necks), obesity, malignancy or a previous episode of DVT, and women taking oral contraceptives. Results of several prospective, randomized clinical trials have shown that in patients in whom abdominal or thoracic surgical procedures are done, most venous thrombi detected by ^{125}I fibrinogen scan can be prevented by the administration of low (mini) dose heparin. The value of this prophylactic method in major hip operations or suprapubic prostatectomy has not been settled.

Since pulmonary embolization is the primary reason for prophylactic anticoagulation, and since the incidence of DVT is at least ten times greater than the incidence of major pulmonary embolism, some authors have questioned the significance of these findings. In a recently published international study, however, it was found that low dose heparin prophylaxis significantly reduces deaths from pulmonary embolism in postoperative patients.

The technique involves the subcutaneous administration of 5,000 units of sodium heparin every 8 to 12 hours before operation and continuing for five to ten days postoperatively or until the patient is fully ambulatory. Heparin administered in this fashion does not significantly change the results of coagulation tests. Its mechanism of action is thought to be inhibition of activated factor X, which plays a key role in both the intrinsic and extrinsic clotting systems. There has been a slightly increased incidence of wound hematoma associated with the use of low dose heparin, and a slight increase in transfusion requirements.

Contraindications to the use of prophylactic heparin are similar to those for therapeutic anticoagulation. Other methods of prophylaxis which have been shown to be effective in reducing the incidence of DVT include oral administration of anticoagulants, use of pneumatic compression or galvanic stimulation of the calf muscles during operation, and infusion of dextran, but none of these is as effective as low dose heparin administration. Therapy with low dose heparin is also the simplest and cheapest method, since laboratory control is not necessary.

It has been estimated that the widespread use of this regimen would save between 4,000 and 8,000 lives each year in the United States alone, and surgeons should therefore be encouraged to use it in high risk patients over the age of 40 in whom major abdominal, pelvic or thoracic surgical procedures are done.

JERRY GOLDSTONE, MD

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Skillman JJ: Postoperative deep vein thrombosis and pulmonary embolism. Surgery 75:114-122, Jan 1974

Tumor-Estrogen Binding Determination in Patients with Breast Cancer

WHEN SUCCESSFUL, ablative endocrine procedures can give dramatic responses in patients with metastatic breast cancer. The combined early use of simultaneous adrenalectomy and oophorectomy with multiple drug chemotherapy may offer the most dramatic and prolonged response for these patients. Although in skilled hands adrenalectomy can be done with safety and excellent toleration, it is too major a procedure unless a significant response rate is achieved.

The response rate has been unreliable when based on clinical associations, cell type of tumor, disease free interval or previous endocrine response.

A test such as tumor estrogen binding, that accurately predicts a response to endocrine ablation is a significant advancement in the selection of patients for such procedures. Measurement of tumor estrogen binding capacity is based on incubating the fresh tumor with radioactive estradiol and determining the binding capacity. Various investigators have determined that in about 50 percent of cases of human breast cancer there is positive binding. In patients with negative binding, few if any responses to endocrine ablation occur. In more than 50 percent of patients with positive estrogen binding, there will be a response following bilateral adrenalectomy and oophorectomy.

A portion of all primary tumors when excised should be stored in liquid nitrogen and sent for estrogen binding determination. Metastatic lesions should also be obtained for estrogen binding determination. Patients with positive estrogen binding should have endocrine ablation (adrenalectomy and oophorectomy) combined with nonhormonal chemotherapy.

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Aortoenteric Fistula

WITH THE INCREASED use of prosthetic grafts for repair of aortic aneurysms and occlusive atherosclerotic diseases, aortoduodenal or enteric fistulas are an often fatal and yet potentially correctable complication. The suggested factors in the development of such fistulas include inadequate apposition of the prosthetic graft to the host aorta, failure of interposition of a tissue barrier between the two structures and graft sepsis. Also fistulas have occurred between aortic aneurysms and the duodenum; clearly the prosthetic graft cannot be implicated in all instances. The initial presentation is often in the form of upper gastrointestinal hemorrhage in small amounts and may occur even up to a year after aneurysmectomy. Often a delay in diagnosis is synonymous with a fatal outcome. The morality rate ranges from 25 to 70 percent. Treatment may be either by circumvention with axillo-femoral bypass or by prosthetic graft replacement. Prosthetic graft replacement, however, is not indicated if the fistula is due to infection. Awareness of the condition in any patient with upper gastrointestinal blood loss and previous prosthetic abdominal aortic graft should lead to early surgical intervention and salvage of an otherwise fatal condition.

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EDITORIALS

Informed Consent—An Unreality?

ELSEWHERE IN THIS ISSUE is an article documenting the relative uselessness of the legal doctrine of informed consent in accomplishing its intended purpose. Informed consent discussions are not well remembered by patients (in fact they may even generate complications which would otherwise not have occurred) and it turns out that they do not usually provide any help in protecting a doctor who is sued in a malpractice case. None of this will come as any surprise to experienced physicians. The human mind, at least the conscious mind, is not like a tape recorder which automatically takes down everything that is heard and remembers it exactly as it was heard. Rather the human mind is more selective. It tends to hear and remember what it wants to hear and remember, and not to hear, or to forget, what might be disturbing or threatening. And it may pay no attention at all and hear nothing if it happens to be occupied with something else.

Informed consent may prove to be yet another of those situations in which the assumptions of the legal system run counter to the realities of human nature and human biology. If so, it will once more be shown that attempts to make biological reality out of legislative or judicial fiat fail, and only produce something that is unreal. And if informed consent turns out to be such an unreality, it follows that efforts at its legal enforcement will eventually fail and in the process add further to the time, energy and dollars spent unnecessarily in health care.

And so, what else is new?

—MSMW

Crohn's Disease

MORGAGNI MAY HAVE described this entity in 1761;[1] however, it remained for Crohn and his associates to describe the clinical and pathological features of terminal ileitis.[2] Although the concept of regional enteritis originally referred to the terminal ileum, it soon evolved to include the remainder of the ileum and jejunum. Duodenal involvement was reported in 1937.[3] Granulomatous involvement of the stomach was reported in 1949[4] and 1950.[5] Involvement of the esophagus was reported in 1954.[6] Although reports of colonic involvement of Crohn's disease appeared shortly after Crohn's original description in 1932, colonic involvement was shown to occur conclusively in 1960.[7] Crohn's disease of the mouth was reported in 1969.[8] Therefore, in a few years from Crohn's description involving the terminal ileum the concept of the disease changed to include all segments of the bowel from mouth to anus. The disease may occur as an isolated lesion in any segment of the bowel or as multiple lesions in the bowel. The ileum remains the principle site of the disease either alone or with involvement of the colon and jejunum.[9,10]

The clinical presentation of patients with Crohn's disease is highly variable. This is readily understandable when one considers that the presenting complaint may be due to involvement of any one or multiple areas of the bowel, systemic toxicity of the disease, obstruction of the intestinal lumen, impairment of intestinal absorption, intestinal complications such as perforation or fistulization (or both) or extra-alimentary complications such as arthritis, spondylitis, uveitis, hydronephrosis or dermal, hepatic or renal disease.

Atwell and co-workers reviewed the cases of 212 patients with Crohn's disease presenting to the General Infirmary at Leeds.[9] Abdominal pain was the presenting complaint in 61 patients, and an abdominal mass was present in 27 of these 61 patients. Diarrhea was the initial complaint in 41 patients; 18 of these 41 patients presented with an abdominal mass. Associated symptoms and signs were vomiting, loss of weight, blood and mucus in the stool, anemia, constipation, abdominal distension and arthritis. Forty-three patients presented with clinical features consistent with acute appendicitis. Twenty-seven patients presented with complications of the disease; that is, intestinal obstruction, perianal disease, fistulae, arthritis and fever.

In this issue of the WESTERN JOURNAL Dr. Burbige brings our attention to one of the least common presentations of Crohn's disease: isolated granulomatous involvement of the stomach.

The clinical significance of this lesion is in its distinction from peptic disease or malignancy of the stomach, and in its propensity for upper gastrointestinal tract obstruction.

The distinction from peptic disease and carcinoma is supported by evidence of regional enteritis elsewhere in the gastrointestinal tract.[10,11] Further support is obtained from findings on gastric cytology, endoscopy and biopsy.[12] Occasionally laparotomy may be necessary to establish the diagnosis. The case reported by Dr. Burbige illustrates the difficulty in distinguishing Crohn's disease from carcinoma. The value of endoscopic biopsy was shown only in retrospect but serves to illustrate the potential of this procedure for definitive diagnosis in this form of the disease.

Repeat gastroscopy one year after diagnosis in this case showed remarkable improvement. The potential for improvement, either as the natural course of the disease or as a consequence of medical therapy, encourages a conservative approach to this problem. In those instances of refractory obstruction, a bypass surgical procedure has been successful in relieving the obstruction.[13] The reluctance toward early and extensive surgical operation in any patient with Crohn's disease becomes more reasonable when one reviews the results of operations in Crohn's disease. One is discouraged by the reported recurrence rate of approximately 50 percent.[9] Data such as these tend to discourage surgical management of Crohn's disease unless it is compelled by serious complications or a deteriorating course of the illness.

The reported improvement in Dr. Burbige's patient affords the opportunity to speculate on the relationship of the therapy and the possible cause of this disease. Could there have been response in this patient to the antimicrobial and adrenal steroid therapy? Several authors have reported on the possibility of infection as a cause of this disease. There are reports of the induction of histopathological changes similar to those of Crohn's disease in experimental animals.[14,15] Electron microscopic studies have been reported to show microorganisms in the lamina propria and submucosa of diseased colon with Crohn's disease.[16] The isolation of bacterial variants of pseudomonas from tissues involved with Crohn's disease has been reported.[17] Viral isolation and a tissue culture system enabling replication and characterization of a virus isolated from tissue involved with Crohn's disease have also been reported.[18,19]

Although these findings are at variance, the efforts are encouraging and show promise of eventually understanding the cause of this disease.

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Testicular Tumors

ELSEWHERE IN THIS ISSUE appears a timely Specialty Conference on testicular tumors. In recent years great advances have been made in our understanding of these tumors but much work remains to be done in epidemiology, detection and diagnosis, and pathology and treatment.

Three aspects of epidemiology deserve mention. While the annual age-adjusted incidence rates for all races is three per 100,000, Twito and Kennedy[1] have shown that in the 15- to 34-year-old age group testicular tumors are the most frequent malignancy. In men 35 to 59 years old, while lung tumors take precedence, testicular tumors account for seven per 100,000, which is more than double the rates in the general population.

A doubling of morbidity rate has been reported in comparing the 1943-1947 period with the 1958-1962 period (Clemmesen).[2] A similar trend in the United States has been suggested by Grumet and McMahon.[3] Testicular tumors are extremely rare among blacks under the age of 45 with the ratio of about one to six in comparison with whites. No comprehensive study of environmental factors responsible for these observations has been carried out.

Compared with the publicity about breast examination in women, to date no effort has been made to alert young men to examine their scrotums for a nodule, enlargement or change in consistency. Men rarely feel their scrotums and if there is any abnormality the patient is reluctant to consult a physician. Once he has consulted a physician there is often a long delay in orchiectomy with tragic consequences for the patient. Borski has called attention to the fact that there is a six-month delay between diagnosis and treatment.[4]

The clinical classifications used in the United States have almost completely ignored the local extent of the tumor and tumors confined to the scrotum have generally been categorized as stage A. The International Union Against Cancer (Union Internationale Contre Cancer, or UICC) has had a Commission on Clinical Stage Classification of Tumors, headed in succession by Dr. Perry (USA), Prof. Denoix (France), Mr. Harmer (UK) and Prof. van der Werf (Holland). This commission has had several subcommittees on urological tumors and has published a clinical classification of these tumors which has been adopted by the American Joint Committee on Clinical Stage Classification of Tumors:

UICC Clinical Classification of Testis Tumors

T1 - Tumor limited to the body of the testis
T2 - Tumor extending beyond the tunica albuginea
T3 - Tumor involving the rete testis or epididymis
T4 - Tumor invading the spermatic cord and/or scrotal wall
  T4a - Invasion of spermatic cord
  T4b - Invasion of scrotal wall

The details of this classification are available in a UICC publication[5] and a report by Mr. David Wallace.[6] It should be noted that the T categories of UICC are subclassifications of stage A of Dr. Thompson's as presented in this conference.

The first serious effort to classify testicular tumors according to histology was made by Friedman and Moore.[7] This was, in fact, Dr. Friedman's classification and, happily, he has been a participant in the conference. Friedman and Moore's study was followed by a report by Dixon and Moore,[8] who correlated pathology with behavior. In the report of survival and mortality of patients with testis tumors these authors grouped the tumors into five categories: pure seminoma; embryonal carcinoma with or without seminoma; teratoma pure or with seminoma; teratoma with either embryonal carcinoma or choriocarcinoma or both, and with or without seminoma; choriocarcinoma pure or with seminoma or embryonal carcinoma or both. This classification has resulted in some confusion because it has been interpreted as a histological classification which it was not intended to be. Mostofi (1973)[9] modified this classification emphasizing the need for precise identification and listing of each element in the tumor. In the meantime the situation has become more complicated by the fact that there also have developed British, French and Russian pathological classifications. Since these classifications cannot be equated with each other it has been impossible to compare incidence and prevalence rates, survival and mortality rates and results of therapy.

The World Health Organization (WHO), in its program of arriving at standard classifications of tumors of various sites, has endeavored to create a standard histopathological classification of testis tumors. Understandably, the problem was quite difficult to solve because pathologists tend to become emotional about any classification they happen to use. To WHO's credit it should be said that all the protagonists, including Prof. Cabanne (France), Prof. Ganina (USSR), Dr. Mostofi (USA), Dr. Pugh (UK), Prof. Teilum (Denmark) and a number of other pathologists were brought together and after two conferences a simple classification based entirely on histology was devised. The details of classification have been published by WHO (1977).[10]

The WHO classification[10] subdivides germ cell tumors into tumors of a single histological pattern and those with more than one histological pattern. The former includes seminoma, spermatocytic seminoma, embryonal carcinoma, yolk sac tumor (embryonal carcinoma, infantile type), pure choriocarcinoma and teratoma. Teratoma may be mature or immature, or teratoma with malignant areas not recognizable as any of the above but with squamous cell carcinoma, adenocarcinoma

or carcinoid, and so forth. In about 40 percent of germ cell tumors more than one histological type is present. The WHO classification recommends that the specific histological types be listed; for example, teratoma and embryonal carcinoma, choriocarcinoma and teratoma.

It may well be asked why we should have a new pathological classification. Actually, the WHO classification is not a new classification. It is a more systematic listing and more precise definition of the major basic histological types—seminoma, embryonal carcinoma, choriocarcinoma and teratoma—and whether they occur in pure form or admixtues and, if so, the precise types that are present. Two other histologic types are also listed—spermatocytic seminoma and yolk sac tumor—but these are rarely seen in young men.

It may be argued that by the time an investigator classifies his cases according to this classification the number in each category will be too small for statistical purposes. But the structure, behavior and treatment of each of these main categories (seminoma, embryonal carcinoma, choriocarcinoma and teratoma) are so different that any pathological classification that lumps any of these together is worthless. The WHO effort in subdividing teratomas into mature and immature teratoma is especially desirable because we do not know whether there is any difference in the behavior of these two categories which have, to date, been buried under teratoma.

Since 40 percent of testicular tumors show more than one histological pattern and a tumor of one pattern may show a totally different pattern in the metastasis, it is essential that the orchiectomy specimen be thoroughly investigated not only in the neoplastic but in nonneoplastic areas as well. Furthermore, the remaining wet tissue should be saved for at least seven years. This is highly desirable because if late metastasis of a different pattern develops in a patient, one can go back to the original primary specimen for possible explanation of the apparent dichotomy.

Some work is being done on histological demonstration of chorionic gonadotropins and alpha fetoproteins on fixed tissue. But there is great need for application of modern techniques of histology to these tumors: histochemistry, tissue culture, fluorescence microscopy, transmission and scanning electron microscopy. These techniques require immediate and proper handling of the specimen.

One of the most important and least studied areas is endocrinology of testicular tumors. The commendable policy of immediate orchiectomy has often resulted in incomplete hormone assays. Spermatic vein blood, which can easily be collected at the operating table after ligation of spermatic artery, yields a more accurate determination of the exact type of hormone produced than does blood from general circulation. Radioimmunoassay has provided a more delicate quantitation of the hormones and this is especially valuable in follow-up of patients after orchiectomy.

Still another area for research is correlation of histology with hormone level. How much chorionic gonadotropin producing tissue must be present to give what level of hormone in the assay. It is essential that the precise structure of the tumor be identified and the components listed and quantitated so that they can be correlated with hormone levels.

The large scale introduction of chemotherapy in treatment of testicular tumors has opened a new era in dealing with these tragic tumors. Embryonal carcinoma, choriocarcinoma and tumors in which these two elements are present are most amenable to chemotherapy, as discussed elsewhere in this Specialty Conference. Here again, the exact histological types of tumor should be listed to alert radiotherapists and chemotherapists of the situation as it exists and to enable them to make proper evaluation of the results as to tumor type and agent.

One area that demands special attention is the discovery of one or more agents that alone or in combination can result in transforming embryonal carcinoma with or without other elements to a mature teratoma which could then be surgically excised.

In conclusion, two points merit emphasis; there is urgent need for standard nomenclature in clinical and pathological diagnosis and classification, and there is great need for research on epidemiology, etiology, structure and behavior of testicular tumors in man.

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Derzon to DHEW

ONCE AGAIN California and the West are sending an unusually able health professional to an important post in the government in Washington. Robert A. Derzon is a skilled and experienced administrator intimately familiar with the heartaches and triumphs of patient care, and the problems and challenges of education and research in the health sciences. He brings his intellect, his warm compassion and his considerable fiscal skills to the Health Care Financing Administration (HCFA), a newly created division of the Department of Health, Education, and Welfare (DHEW), as its first Administrator. He has stated:

> A real issue in this decade will be whether health professionals can set aside their self-interest to concentrate on the ways in which we can increase the health of our population. Hopefully, we can advise our sick patients to become prudent and judicious users of our expensive but vital hospitals and our health care resources. Government and the private sector must coalesce in finding ways to moderate the escalation in health care costs by assuring access to pluralistic and diverse health care systems, while maintaining high standards and humane service.

It is the interest of all concerned to achieve these goals. The nation should be well served with Bob Derzon in a position of leadership to accomplish them. He deserves and will need the help of us all.

—MSMW

Fibrosing Alveolitis

—Extrinsic Allergic and Cryptogenic

THE TERM "fibrosing alveolitis" has been coined by John G. Scadding of England as a generic name for the disease that had been described under such names as interstitial pneumonia or pneumonitis, acute or chronic Hamman-Rich disease or syndrome, idiopathic interstitial fibrosis, chronic diffuse sclerosing alveolitis, organizing interstitial pneumonia and usual interstitial pneumonia. Fibrosing alveolitis has been subdivided into two groups: extrinsic allergic alveolitis (typified by farmer's lung) and cryptogenic fibrosing alveolitis. In this country extrinsic alveolitis is referred to as "hypersensitivity pneumonitis"; whereas, cryptogenic fibrosing alveolitis is commonly called "idiopathic pulmonary fibrosis." A number of clinical, radiographic, immunologic and histologic features enable these two forms of "fibrosing alveolitis" to be clearly differentiated.[1]

Extrinsic allergic alveolitis is characterized by an acute or insidious onset of dyspnea, malaise, fever, muscle pains and weight loss. There is a history of frequent and regular inhalation of some organic allergen. Auscultation of the lungs may show fine crepitations. On roentgenograms of the chest, diffuse nodular infiltration with a tendency to involve mid- and upper lung fields may be seen. Fibrosis when it occurs mainly involves the upper lobes. Precipitating antibodies in the serum, belonging to immunoglobulins G (IgG) class, against the relevant allergen are usually present. Analysis of bronchial lavage fluid shows a striking increase in T-lymphocytes and immunoglobulin M (IgM) along with some eosinophils and IgG.[2] In early disease histologic examination of the lung tissue shows noncaseating granulomata, but in the advanced stage, granulomata are replaced by fibrous tissue. Corticosteroids are effective in the early stage before fibrosis is established.

Cryptogenic fibrosing alveolitis or idiopathic pulmonary fibrosis differs from the extrinsic type in many ways. Dyspnea on exertion is the constant symptom but fever, muscle pains and weight loss are absent. Clubbing of the fingers and toes occurs in as many as 70 percent of the patients and crepitant rales are present in more than two thirds of the patients. Radiological appearance varies with the stage and extent of the disease and includes ill-defined patchy opacities, nodular infiltrates, linear and reticular shadows, "ground glass" appearance and honeycombing. Unlike extrinsic allergic alveolitis the roentenographic abnormality is diffuse. Lung function studies show reduction of static lung volumes and diffusing capacity for carbon monoxide but the degree of fibrosis is best correlated with the change in arterial oxygen tension and alveolar-arterial oxygen difference on exercise and the coefficient of lung retraction (maximum static transpulmonary pressure/observed total lung capacity).[3] Immunologic

studies show clear evidence of a T-cell mediated process against collagen in this disease.[4] In about two thirds of the patients, antinuclear factor, or rheumatoid factor, or both, are present in the serum. Furthermore, cryptogenic fibrosing alveolitis is accompanied in a proportion of patients by certain other autoimmune disorders; for example, Sjögren syndrome, Hashimoto thyroiditis, chronic active hepatitis, polymyositis and hyperglobulinemic renal tubular acidosis.[5] The occurrence of familial cases and some preliminary data indicating an increase in HLA-12 and HLA-29 in patients suggest that there may be a genetic predisposition to cryptogenic fibrosing alveolitis.

The histopathologic features can be described in a range between two extreme patterns which may be called cellular and fibrotic (Scadding and Hinson prefer terms desquamative and mural, respectively[6]). The cellular pattern is characterized by the presence of inflammatory cells mainly lymphocytes, macrophages and plasma cells. Eosinophils and neutrophils are also noted. The fibrotic pattern is distinguished by the prominence of alveolar wall thickening and fibrous tissue with fewer inflammatory cells. Recent studies suggest that the process starts as an alveolitis and progresses to interstitial fibrosis.[4] Once the disease has reached the fibrotic or mural stage it probably becomes irreversible, but the cellular or desquamative stage can be successfully treated in many cases with corticosteroids. Immunosuppressive drugs have been found useful in some cases but their role in the management of cryptogenic fibrosing alveolitis remains uncertain.[7]

In all cases of fibrosing alveolitis or diffuse interstitial fibrosis the possibility of extrinsic allergic alveolitis should be considered. Once the diagnosis is firmly established, institution of corticosteroid therapy and avoidance of offending allergen can bring the favorable outcome. If the clinical, radiographic and immunologic features point to the diagnosis of cryptogenic fibrosing alveolitis, a lung biopsy may be justified to stage the disease because corticosteroids if given in cellular or desquamative cases may prevent formation of fibrosis. Further clinical trials, however,[7] are needed to establish the value of lung biopsy as a guide for selecting therapy in patients with cryptogenic fibrosing alveolitis.

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CASE REPORTS

Refer to: Burbige EJ: Crohn's disease of the stomach. West J Med 126:397-400, May 1977

Crohn's Disease of the Stomach

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ALTHOUGH CASES had been described previously,[1] it was Crohn, Ginzburg and Oppenheimer who, in 1932, first recognized nonspecific granulomatous inflammation of the ileum as a separate disease entity.[2] They described 14 patients with the disease limited to the terminal ileum and hence the name regional ileitis was coined. However, since that time it has been shown that this nonspecific granulomatous process may involve many different sites in the alimentary tract from the mouth[3] to the anus.[4] In the last decade there has been an increased recognition of gastroduodenal involvement by Crohn's disease.[5-15]

Recently a patient was seen who initially was thought to have gastric carcinoma. The subsequent finding that she had a granulomatous involvement of the stomach prompted this review of the literature and consideration of some of the clinical features of the disease and methods of treating this disorder.

Report of a Case

A 42-year-old white woman, a hospital employee, had been in good health until March 1972. At that time excisional breast biopsies were done for fibrocystic disease. Shortly after the procedure she began to notice episodes of nausea, vomiting, anorexia and weight loss. By the time she presented to the outpatient department in December 1972, she had lost 30 pounds and complained of almost continuous epigastric gnawing pain. This pain was somewhat relieved by taking antacids. However, the episodes of nausea and vomiting had increased in frequency to the point that she was unable to eat without vomiting.

Figure 1.—Upper gastrointestinal series showing irregularity of the antrum and narrowing of the pylorus.

On physical examination, the patient was seen to be thin and appeared chronically ill. Aside from epigastric tenderness, the examination showed no abnormalities. Laboratory studies disclosed the following values: hematocrit, 38 percent; leukocyte count, 9.9×10^3; normal values for thyroxine (T-4), blood urea nitrogen, serum electrolytes, glucose and calcium; cholesterol, 152 mg per 100 ml; total protein, 6.6 grams per 100 ml, and albumin 3.8 grams per 100 ml. A Venereal Disease Research Laboratories test and an intermediate purified protein derivative were negative. No abnormalities were seen on an x-ray film of the chest.

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Submitted, revised, August 5, 1976.

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Figure 2.—Spot film from the patient's upper gastrointestinal series showing pronounced narrowing of the antrum and pylorus.

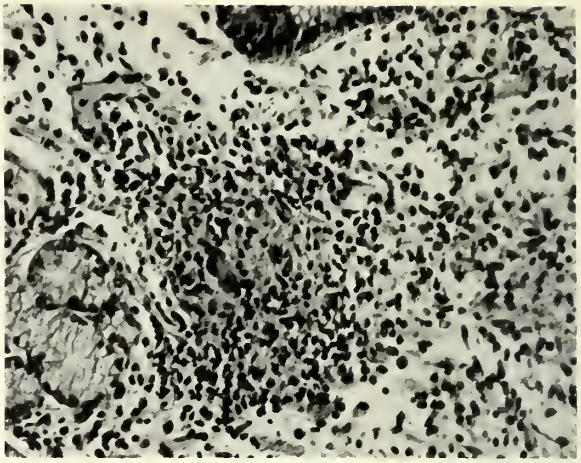

Figure 3.—Gastric biopsy specimen obtained by fiberoptic endoscopy showing antral mucosa and a focus of nonspecific granulomatous inflammation. (Hematoxylin and eosin; magnification, X240.)

An upper gastrointestinal series (Figures 1 and 2) showed pronounced antral deformity and decreased peristalsis. The findings were thought to most likely represent carcinoma of the stomach, with scarring secondary to peptic ulcer disease a less likely possibility. To resolve the uncertainty, endoscopy was done as an outpatient procedure. As the endoscope entered the stomach a moderate amount of retained secretions was encountered. The antrum was notably narrowed and contracted poorly. In the distal antrum, the mucosa was rigid and nodular with multiple ulcerations, some having a stellate appearance. The pylorus was narrowed and did not open sufficiently to allow the endoscope to be passed into the duodenum. Biopsy specimens and brushings for cytology were obtained.

Because of the presence of obstruction, the patient was admitted to the surgical service and treated with nasogastric suction. The preliminary reports of the pathology specimens were negative for tumor. At laparotomy the changes were consistent with peptic disease and a pyloric channel ulcer was described. A vagotomy and Finney pyloroplasty were carried out. Immediately postoperatively the patient did well and had no further problem with gastric retention. Later, examination of serial sections of the original biopsies (Figure 3) obtained at endoscopy showed foci of nonspecific, noncaseating granulomata with giant cells, consistent with Crohn's disease.

At first the patient did well and began to gain weight. However, she soon began to have problems with diarrhea, abdominal bloating, distention, lack of further weight gain, and foul smelling eructations. Upper gastrointestinal and small bowel series showed deformities of the pylorus and duodenum consistent with the surgical procedures carried out. The terminal ileum appeared to have irregular mucosa suggestive of inflammatory bowel disease. A barium enema study showed a normal colon with reflux into a normal terminal ileum. Because the patient's symptoms were thought to be due to active Crohn's disease, therapy was started with sulfasalazine (Azulfidine®), 500 mg three times a day, and prednisone, 30 mg every other day tapered to a maintenance dose of 20 mg every other day. Within one week of starting therapy, the diarrhea decreased and the other symptoms improved. Subsequently the patient has become asymptomatic. Repeat endoscopy after one year showed a postoperative stomach with grossly normal appearing mucosa. On random biopsy, only chronic inflammation was found. The patient continues to do well after 42 months with only periodic episodes of diarrhea.

Discussion

Granulomata have been found in a variety of diseases: sarcoidosis, tuberculosis, syphilis, catscratch fever, chronic ulcerative colitis, regional enteritis, berylliosis, silicosis, foreign body reactions, leprosy, brucellosis and histoplasmosis. In a review of the literature concerning granulomatous involvement of the stomach, several trends become evident. As in the original description of granulomatous involvement of the ileum, much debate and ascription to other diseases has oc-

curred. Fahimi[16] suggested that there were three different groups of patients. Group I comprises patients with documented granulomatous disease of the stomach with associated signs of sarcoid elsewhere. Group II is made up of patients with granulomas in the stomach and involvement of the bowel elsewhere which resembles regional enteritis. He also suggested a third group to be recognized as a distinct clinical entity, namely, those with isolated granulomatous gastritis in which there was gastric involvement only, with no signs of regional enteritis or sarcoidosis.

There have been many reports of gastric involvement by sarcoidosis.[16-19] If, as in the case reported by Orie,[17] there is pulmonary involvement and evidence of systemic disease, then it is reasonable to assume that granulomas encountered in the stomach are related to the sarcoid process. Likewise, the findings of granulomas in the stomach and involvement of bowel elsewhere warrants the diagnosis of Crohn's disease. The finding of isolated gastric granuloma without systemic disease makes the diagnosis of sarcoid or Crohn's disease less definite since the histology of the sarcoid granuloma is nonspecific.[20] Response to therapy cannot be used since both diseases behave similarly.

The first report that recognized granulomatous involvement of the stomach to be related to Crohn's disease was that by Ross.[5] Since then there have been more than 50 cases reported.[5-15] In considering the cases where sufficient data are available, there are several interesting aspects which clinically may help distinguish this involvement of the stomach by Crohn's disease.

Age and Sex

The youngest patient was 9 years old when diagnosis was made. The disease probably already had been present for some time. The oldest patient was 60 years old. The average age was 27 years. It should be noted that this is approximately the average age of onset of Crohn's disease elsewhere in the alimentary tract.[21] About two thirds of the patients reported were male.

Clinical

The two most common complaints in this group of patients were epigastric pain and weight loss. Nausea and vomiting were present in a large number, most often when obstruction was present. Diarrhea was present in about half of the patients. This feature occurred most often in those with involvement of other segments of bowel as well.

Radiologic

The most common findings on x-ray studies were decreased peristalsis, dilatation of the stomach and irregularity of the antrum. The radiologic diagnosis made most often was carcinoma of the stomach. Characteristic changes elsewhere in the bowel would suggest involvement of the stomach by Crohn's disease rather than carcinoma. In this review, in all but five of the cases there were findings of Crohn's disease elsewhere and in more than two thirds there was involvement of the duodenum.

Pathology

The pathologic findings are similar to those in Crohn's disease found elsewhere in the alimentary tract. In most cases biopsy specimens were obtained at surgical operation. The first report of a biopsy study showing a granuloma obtained through the biopsy channel of the fiberoptic endoscope was by Roseman.[9] Since then, there have been four additional cases.[10-12] The difficulty in obtaining biopsy specimens containing granuloma has been well pointed out by Danzi and coworkers.[11] However, the yield of granulomas can be increased by biopsy of microulcerations.[22] As in this case, examination of serial sections is also important.

Endoscopy

The findings at endoscopy were similar. These consisted of deformity of the antrum with narrowing, pale mucosa, cobblestone mucosa, mucosal inflammation and superficial ulceration. In addition, in some patients there were a nodular mucosa and polypoid masses with ulceration, either longitudinal fissures or stellate ulcerations.

Treatment

In most reported cases, surgical operation was done at some time in their course. Most operations were exploratory laparotomies or procedures for relief of gastric outlet obstruction. Course after operation was not predictable. Which is the best type of surgical procedure has not yet been resolved because of the limited number of cases and the difficulty in making the diagnosis preoperatively; the most popular surgical approach at present seems to be vagotomy and by-passing

gastroenterostomy.[23,24] The medical treatment of the disease is similar to that described for Crohn's disease in general.[25,26] The response to therapy with steroids is usually favorable and pyloric obstruction may be relieved without surgical intervention.

It seems that with a better understanding of the clinical signs and symptoms and a wider use of fiberoptic endoscopy and biopsy, more cases will be identified before operation and patients will be given a chance to improve as a result of steroid therapy alone.

Summary

In a patient thought to have carcinoma of the stomach on the basis of clinical and radiographic findings, fiberoptic endoscopy with biopsy was done for confirmation of the diagnosis. The patient was found to have Crohn's disease of the stomach. The average age of patients with this disorder is 27.3 years and two thirds are males. The presenting manifestations include epigastric pain, weight loss, nausea and vomiting. Radiologic findings are antral deformity and poor peristalsis of the stomach. Although in most patients with Crohn's disease of the stomach the disease also is present in other parts of the body, there may be isolated gastric involvement. Fiberoptic endoscopy with biopsy can establish the diagnosis of Crohn's disease of the stomach simply and safely.

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Refer to: Rollo FD, Cavalieri RR: Lingual thyroid in two members of a family. West J Med 126:400-403, May 1977

Lingual Thyroid in Two Members of a Family

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LINGUAL THYROID is a consequence of anomalous thyroid development. The frequency of this condition has been estimated to be approximately one in 4,000,[1,2] but the prevalence of lingual thyroid among asymptomatic euthyroid persons is not known. There is a high female to male ratio; in one series 87 percent of the cases were female.[3] According to one author,[4] about 15 percent of patients with this condition are hypothyroid. There has been one report of lingual thyroid in two siblings.[5] To our knowledge, no other instances of familial occurrence of this condition have been described. However, other types of developmental abnormalities of the thyroid have been noted among relatives of patients with lingual thyroid.[3,5]

This report describes the occurrence of lingual thyroid in a father and his son. The former was clearly hypothyroid by clinical and laboratory

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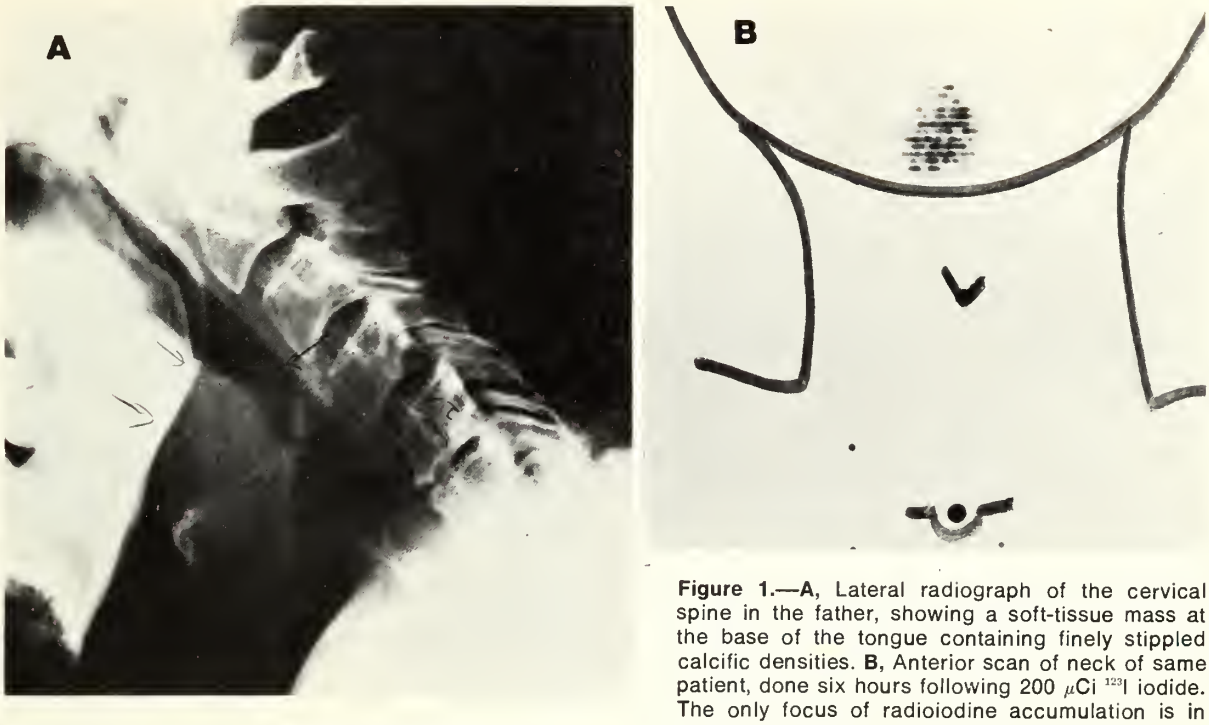

Figure 1.—A, Lateral radiograph of the cervical spine in the father, showing a soft-tissue mass at the base of the tongue containing finely stippled calcific densities. **B,** Anterior scan of neck of same patient, done six hours following 200 μCi ^{123}I iodide. The only focus of radioiodine accumulation is in the lingual region.

criteria; in the latter there was laboratory evidence of hypothyroidism.

Reports of Cases

In a 52-year-old man, lingual thyroid was suspected when calcification was noted below the angle of the mandible on cervical spine radiographs obtained following a minor automoblie accident (Figure 1A). The patient reported that during the preceding two years he had noted progressive loss of energy, cold intolerance, increased sleep requirements, and dry skin. The patient had been told that at the age of 12 a small thyroglossal duct cyst was removed. On examination, blood pressure was 120/80 mm of mercury and pulse rate was 80 beats per minute. Significant physical findings included: dry, scaly skin over the extremities; coarse, somewhat brittle hair, absence of a palpable thyroid gland in the neck. A well-healed 1 cm long surgical scar was noted on the patient's neck in the midline 2 cm above the thyroid cartilage. On direct laryngoscopy, a 2 by 2 cm mass on the dorsum of the tongue was noted.

Thyroid function tests showed low total serum thyroxine and free thyroxine index,[6] a slightly elevated serum triiodothyronine level (by radioimmunoassay) and an elevated serum thyroid-stimulating hormone (TSH) value (Table 1). Thyroid radioiodine uptake (^{123}I) values were 3 percent at 2 hours, 5 percent at 6 hours and 7 percent at 24 hours (all low). These results were obtained with the scintillation detector placed over the region of the base of the tongue. Thyroid scans were done at six hours following oral administration of 200 μCi of ^{123}I iodide. No functioning thyroid tissue was visible in the neck, but radioiodine accumulation was noted in the region of the posterior aspect of the tongue (Figure 1B).

On the basis of the clinical history and the thyroid function test results, the patient was considered to be hypothyroid and was given L-thyroxine. Two months later while on a maintenance daily dose of 0.2 mg of L-thyroxine, the serum TSH was 2.3 μU per ml. He appeared clinically eumetabolic. Six months following the initiation of therapy the lingual mass measured 1.5 by 1.5 cm.

The 9-year-old son of the propositus had been described as a hyperkinetic child and, although he had been given various medications and diets in an effort to control his behavior during the preceding three years, no thyroid abnormality was suspected or investigated. When the father's thyroid condition was discovered, his son was examined.

The boy's pulse was 72, regular, and blood pressure was 110/70 mm of mercury. He was a prepubertal child (height 128 cm, weight 22.4 kg, lower 10th percentile), with normal intelligence. He was

TABLE 1.—*Serum Thyroxine, Free Thyroxine Index, Triiodothyronine, and Thyroid-stimulating Factor (TSH) Concentrations in Three Members of a Family*

Subject	*Age*	*Thyroxine μg/100 ml*	*Free Thyroxine Index*	*Triiodothyronine ng/ml*	*TSH μU/ml*
Father	52	2.6	0.31	2.15	22.
Son	9	6.5	0.46	0.82	17.
Daughter	11	5.8	0.51	1.20	5.2
Normal range		4.5-11	0.5-1.5	1.0-2.0	<6

euthyroid clinically. The thyroid gland was not palpable in the neck. On examination of the pharynx, a 2 by 3 cm pink mass on the posterior dorsum of the tongue was noted. Serum thyroxine and total triiodothyronine values were within normal limits. The free thyroxine index was borderline-low, and the serum TSH level was elevated (Table 1). The radioiodine (^{123}I) thyroid uptake was 6 percent at 2 hours, 8 at 6 hours and 18 at 24 hours. A scan showed all of the radioiodine to be localized to the lingual region (Figure 2). L-thyroxine, 0.10 mg per day, was given. Two months later, the serum TSH level was 3.5 μU per ml. There was no change in the "hyperkinetic" behavior, however. After six months of therapy, the lingual mass was found to have dimensions of 1.5 by 2 cm.

The 11-year-old daughter of the original patient was examined and found to be clinically euthyroid. Her height was 146 cm and weight was 39 kg (upper 75th percentile). Secondary sexual characteristics had already developed but menstruation had not yet occurred. The cervical thyroid gland, on radioiodine scan, was found to be normal. Serum thyroid hormone and TSH levels were normal (Table 1).

The only sibling of the propositus was a sister, age 48. She had been taking thyroid hormone since the age of 2½ years, when a physician noted "failure to develop." She completed high school at age 19, later obtained a master's degree, and is presently employed as a legal secretary. The patient was not available for examination, but her physician for the past 30 years assured us she has a very small palpable thyroid gland in the normal position with no evidence of a lingual thyroid. She is considered to be clinically euthyroid on L-thyroxine, 0.3 mg per day. The parents of the propositus both died in their eighties and were not known to have any thyroid abnormalities. There was no parental consanguinity.

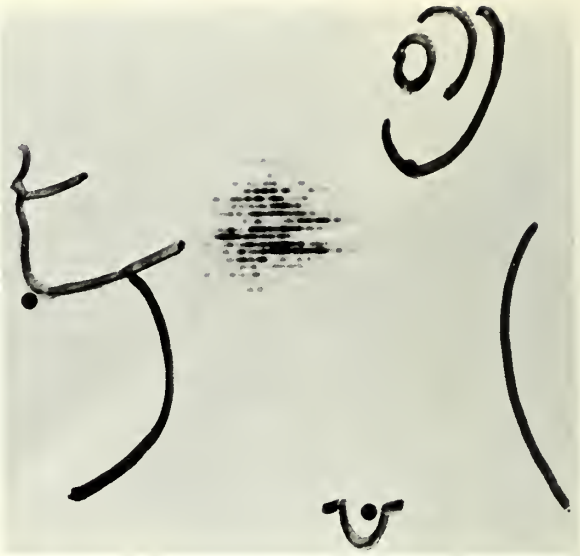

Figure 2.—Lateral scan (^{123}I) of head and neck of the son, showing all of the radioiodine in the lingual region and none in the cervical region.

Comment

Aberrant thyroid tissue may be found, usually in the midline, anywhere from the base of the tongue to the level of the diaphragm. The presence of a lingual thyroid is often suspected on routine oropharyngeal examination or incidentally when a radiograph of the neck is obtained for some other reason, as in one of our patients. A definite diagnosis can be made by scanning following administration of radioiodide. Only one previous instance of familial lingual thyroid has been reported.[5] In that family three siblings had developmental thyroid abnormalities. A brother and sister had lingual thyroids, and another sister had agenesis of one lobe of a cervical thyroid. Our cases represent the first in which two generations of a family had lingual thyroid. Of additional interest is the fact that both of our patients are male; most cases of lingual thyroid have been in females.[3]

Thyroid disorders, including other types of developmental abnormalities, appear to be relatively common among relatives of patients with lingual thyroid. In addition to the case of hemithyroid agenesis described by Orti,[5] Neinas and co-workers have reported that five patients out of a series of 15 cases of lingual thyroid had relatives with one or another type of thyroid disorder.[3] In one of their cases, the daughter of a patient with lingual thyroid had had thyroglossal duct cysts removed in early life.

Early detection of developmental thyroid abnormalities is important in order to prevent hypothyroidism.[7] In our cases, the 9-year-old boy was found to have some growth retardation but little other clinical evidence of hypothyroidism. Presumably, if left untreated, eventually overt myxedema would develop. The serum TSH level was the most abnormal finding of the thyroid function tests in this patient. An elevated serum TSH concentration is generally regarded as a sensitive and early indicator of primary thyroid failure.

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Refer to: Clark RA: Bacterial endocarditis caused by Listeria monocytogenes. West J Med 126:403-405, May 1977

Bacterial Endocarditis Caused by Listeria Monocytogenes

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INFECTION DUE TO Listeria monocytogenes has been reported with increasing frequency in recent years, especially in immunosuppressed patients.[1] However, listeria endocarditis remains extremely rare, with only six cases having been described in the English literature,[2-6] and an additional six cases in French or German (for review see Reference 6). The present report describes a new case of listeria endocarditis and is of particular interest for a history of previous endocarditis, the presence of a presumptive cutaneous source of infection, the development of severe thromboembolic complications and for the description of complete necropsy findings.

Report of a Case

A 67-year-old white woman was admitted to Harborview Medical Center, Seattle, with increasing dyspnea and leg edema. She had been seen on numerous occasions for bilateral leg edema and cellulitis. Similar problems were present in her mother and sister, and she was therefore considered to have Milroy's syndrome of congenital lymphedema. One year previously she had been admitted with fever, sweats, lethargy, confusion, cutaneous petechiae, grade III/VI systolic ejection murmur radiating to the neck and cardiomegaly. Four blood cultures grew Streptococcus viridans, and she was treated with penicillin G, 16 million units per day given intravenously for 17 days. Response was good, although a rash possibly due to penicillin allergy developed late in the course. Six months later increasing congestive heart failure developed; a widened pulse pressure (140/50) and a new grade II/VI decrescendo diastolic murmur along the left sternal border were noted. Blood cultures were negative, and there was response to therapy with digitalis and diuretics.

During the month before admission, progressive dyspnea again developed, and dependent edema worsened. On physical examination at admission, the following findings were noted: temperature, 37.8°C (100°F); blood pressure, 160/50 mm of mercury; respirations 28 per minute; pulse, 110 per minute; bibasilar inspiratory rales; unchanged systolic and diastolic murmurs; pronounced leg edema with extensive cellulitis and ulcerations. Neurologic examination showed no abnormalities, and the spleen was not palpable. Hematocrit reading was 42 percent, leukocyte count was 7,200 per cu mm with a normal differential and erythrocyte sedimentation

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rate was 16 mm per hour. Increased cardiomegaly and pulmonary venous congestion were seen on an x-ray film of the chest. An electrocardiogram showed nonspecific ST and T wave changes. Treatment with oxygen, digitalis, furosemide and heparin initially resulted in improvement.

Cultures of the leg lesions grew a coagulase negative staphylococcus. A blood culture on admission grew a Gram-positive rod on the fourth day. Because of possible allergy, use of penicillins was avoided, and therapy with cephalothin (6 grams per day given intravenously) was begun on day 4. The organism was sensitive to cephalothin and was identified as Listeria monocytogenes on the basis of morphology, tumbling motility at 22°C, slowly developing β hemolysis, catalase positivity and fermentation profiles. Listeria was grown from four more blood cultures obtained on the second and third days. Congestive heart failure worsened despite intensive therapy. Deterioration in mental status prompted a spinal tap on the tenth hospital day which showed the following values: normal pressure; glucose, 119 mg per 100 ml; protein, 36 mg per 100 ml; 2,700 erythrocytes per cu mm; 10 leukocytes per cu mm (60 percent neutrophils). Cultures were negative. Later that day sudden severe dyspnea and cyanosis developed, and the patient died.

On necropsy, the heart was found to weigh 630 grams; bilateral ventricular hypertrophy, dilatation of all chambers and a 200 ml serous pericardial effusion were noted. The aortic valve was thickened, fibrotic and calcified; vegetations were present on all three cusps and contained fibrin, neutrophils and numerous colonies of Gram-positive rods, although cultures of the vegetations grew only a few colonies of Escherichia coli. The mitral valve showed changes consistent with rheumatic heart disease including mild thickening and calcification of both cusps and fusion of the chordae tendineae. There were bilateral pleural effusions, pulmonary congestion and multiple pulmonary emboli with infarction in the right middle and lower lobes. Additional findings included splenomegaly, pronounced passive hepatic congestion and moderately advanced atherosclerosis.

Comment

In this patient, Listeria monocytogenes endocarditis developed on an aortic valve which had been extensively damaged presumably by rheumatic disease as well as the previous episode of streptococcal endocarditis. The clinical findings in this case and in previous reports are not unusual for subacute bacterial endocarditis. Valvular involvement has been limited to the aortic or mitral valves, or both, and in several patients there has been preexisting valvular disease. Thromboembolic complications occurred in this patient as well as in several previously reported cases.[2,3,6] Death was primarily due to progressive congestive heart failure and pulmonary embolization with infarction. Five of the 12 previously reported cases of listeria endocarditis also resulted in a fatal outcome.[6] Of the cases in the English literature, only one other has had autopsy verification of the diagnosis;[3] indeed, the diagnosis was not suspected antemortem in this instance.

Although listeria meningitis has been frequently observed in immunosuppressed patients,[1] endocarditis has in most instances developed in patients without other associated disease. The patient reported had predisposing local factors including the abnormal epidermal barrier and the damaged aortic valve, but there is no reason to implicate a systemic defect in host resistance. Listeria was not cultured from the patient's cellulitis, but these extensive skin lesions represent the most likely portal of entry, although a pulmonary source cannot be excluded. Potential sources of infection were identified in two of the previously reported cases, one of which followed dental extractions[2] and another which was thought to be related to an infected pulmonary infarct.[6] The central nervous system, a common site of involvement in listeria infection did not appear to be affected. Penicillin, ampicillin, erythromycin, tetracyclines and a variety of other antibiotics have been employed in the treatment of listeria infections. Cephalosporins are a reasonable choice in the penicillin allergic patient, but poor cerebrospinal fluid penetration militates against their use when meningitis is present. Their failure in this case may be related to the severity of the cardiac disease or the thromboembolic complications.

Clinicians should be alert to the possibility that endocarditis can be caused by Listeria monocytogenes. In a patient in whom there are appropriate clinical findings, a Gram-positive rod isolated from blood cultures should not be dismissed as a contaminating diphtheroid; the organism must be carefully identified to exclude the possibility of listeria infection.

Summary

A patient described with bacterial endocarditis due to Listeria monocytogenes represents the seventh reported case of this entity in the English literature and only the second case with necropsy findings reported. Interesting features of this case include a history of previous streptococcal endocarditis, a possible cutaneous source of infection and extensive thromboembolic complications. Attention should be drawn to this organism as a potential cause of endocarditis since careful microbiologic evaluation is required for differentiation from common contaminants.

ADDENDUM: Since this manuscript was submitted an additional case of Listeria endocarditis has been reported (Weinstein GS, Nichols NJ, Rogers MR, et al: Endocarditis of aortic valvular prosthesis due to Listeria monocytogenes. Chest 69:807-808, 1976).

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Refer to: Lehman DH: Postdysenteric Reiter's syndrome. West J Med 126:405-407, May 1977

Postdysenteric Reiter's Syndrome

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REITER'S SYNDROME is the triad of arthritis, conjunctivitis and urethritis. The cause of the syndrome is unknown, though persons with the histocompatibility antigen HLA-B27 are clearly at greatly increased risk of Reiter's syndrome developing. In fact, up to 96 percent of affected patients are B27 positive, whereas only about 6 percent of Caucasion controls are positive.[1-9] An infection, either urethritis or dysentery, usually triggers the syndrome in these susceptible persons, although some cases have no apparent preceding infectious episode.[10] The infectious agent is unkown. In North America and England, Reiter's syndrome usually follows nongonococcal urethritis after sexual contact and occurs almost exclusively in young men.[10] The syndrome may also be seen following infectious dysentery, usually shigellosis, particularly in continental Europe, the Mediterranean and Scandinavia.[11] This dysenteric form also occurs primarily in young men but is also seen occasionally in children and women. Reiter's syndrome after dysentery appears to be rare in North America and England.[12] This report documents the occurrence of Reiter's syndrome in a B27 positive woman, after shigellosis developed during a vacation in Mexico.

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Report of a Case

A 23-year-old white woman was admitted to the University of California, San Francisco, Medical Center on July 18, 1975, because of arthritis and conjunctivitis. Two weeks before admission diarrhea had developed while the patient was visiting Baja California. There were as many as 25 slightly blood-tinged, watery stools per day, associated with lower abdominal cramping. One week before admission she was treated with paregoric, with good symptomatic relief. Stool culture was positive for Shigella flexneri. Antibiotics were not given. Four days before admission arthritis began in the left ankle, and the patient's right eye became red and painful. In the next few days painful arthritis developed in the right ankle and both knees, and the left eye became inflamed. The diarrhea had resolved. There was no dysuria or vaginal discharge. The patient had had a single

episode of rheumatic fever at 13 years of age. Family history was noncontributory.

On physical examination the patient was pleasant but in moderate distress from painful arthritis. Her temperature was 38.5°C (101.3°F). There was no rash, and there were no nodules. The conjunctivae were injected bilaterally; there was no keratitis or iritis. A soft pulmonic ejection murmur was heard. The abdomen and pelvis were normal. Both knees and ankles were warm, erythematous, swollen and tender, with obvious effusions. All other joints were normal. Findings on neurologic examination showed no abnormalities.

Laboratory studies disclosed the following values: leukocytes, 12,600 with 64 percent neutrophils, 21 percent lymphocytes and 14 percent monocytes; hematocrit, 37.6 percent; blood urea nitrogen and electrolytes within normal limits; erythrocyte sedimentation rate, 100; 10 to 25 leukocytes per high power field in the urine. No abnormalities were seen on x-ray studies of the chest, and on films of the ankles and knees, effusions only were seen. Sinus tachycardia was shown on an electrocardiogram. Blood, urine, conjunctival, joint fluid, cervical and stool cultures were negative. Arthrocentesis of the left knee showed hazy, yellow fluid with reduced viscosity and no crystals. The leukocyte count was 25,000 with 85 percent neutrophils, 12 percent lymphocytes, 3 percent monocytes; red blood cell count was 2,800. Glucose was 112 mg per 100 ml. Protein was 4 grams per 100 ml. Serum antinuclear bodies (ANA), antistreptolysin O (ASO), Venereal Disease Research Laboratory, rheumatoid factor (RF) and anti-DNA studies all gave negative findings. HLA-B27 was positive. The pyuria resolved by July 27.

The patient's course in hospital was characterized by persistence of arthritis in knees and ankles. The left elbow became inflamed as well, and left peroneal tenosynovitis developed. The conjunctivitis resolved after three weeks. The arthritis improved partially with aspirin and phenylbutazone administration. At discharge on August 12, 1975, arthritis was still present in the patient's left elbow, both knees and ankles, and crutches were required. The erythrocyte sedimentation rate on discharge was 118. On the last follow-up visit on February 26, 1976 (six months after onset of disease), there still was slight residual arthritis in the left ankle, although the patient was no longer taking anti-inflammatory agents. The erythrocyte sedimentation rate was 4.

Discussion

This case was typical of the triad of Reiter's syndrome: (1) polyarthritis with predominantly lower extremity involvement, (2) conjunctivitis and (3) nonbacterial pyuria. The illness began 10 days after dysentery developed due to Shigella flexneri. Postdysenteric Reiter's syndrome occurs most commonly after infection with Shigella flexneri, though it has also been reported secondary to infection with Shigella dysenteriae, paradysenteriae, or Sonnei, Salmonella typhimurium or enteritidis, or after nonspecific diarrhea.[11] Hans Reiter's initial report in 1916 described a German army lieutenant in whom the syndrome developed after an episode of dysentery.[13] Also in 1916 Fiessenger and Leroy described four cases in the French army of the "syndrome conjoctive-uretro-synovial" during an epidemic of bacillary dysentery in Somme, France.[14] Since then the occurrence of Reiter's syndrome after epidemics of Shigella dysentery has been well-documented.[15-19] Two of these epidemics are particularly well known and are worth briefly reviewing here.[18,19]

In a monumental study, Paronen reported 344 cases of Reiter's syndrome during an epidemic of Shigella flexneri dysentery affecting 150,000 people on the Karelian Isthmus in Finland in 1944 (an incidence of 0.24 percent).[18] In two thirds of the cases the syndrome began 11 to 30 days after onset of the dysentery. The occurrence or severity of the Reiter's syndrome did not correspond to the severity of the dysentery. Ninety percent of the affected persons were men and 10 percent women. Almost all (97.5 percent) had arthritis, 89.2 percent had ocular inflammation (conjunctivitis, keratoconjunctivitis, iritis or iridocyclitis), 79.3 percent had urogenital involvement (urethritis, penile lesions, cystitis or nephritis); and the erythrocyte sedimentation rate was elevated in 92 percent. Seventy percent had all three manifestations, 25 percent had two manifestations and 5 percent had only 1 manifestation. Almost all cases of arthritis were polyarticular and involved primarily the lower extremities. The knee was involved in 25.4 percent, the ankle in 16.2 percent of cases—more than twice as often as any other joint. Arthritis almost always persisted after other symptoms had disappeared. It never resolved during the first month but usually resolved during the second to fourth months, though in a fifth, slight

joint symptoms remained when observations were terminated at two months to three years. Ocular and urogenital lesions usually healed within one to four weeks. The present patient's manifestations and course are very similar to those reported by Paronen.

Follow-up study of 100 of Paronen's patients 20 years later showed that only 20 percent were entirely asymptomatic after the first episode.[20] Forty-two percent had permanent disability of some degree, and 32 percent had spondylitis, though usually mild. Three patients were completely disabled. Almost half of all patients, therefore, had long-term sequelae. Of 50 tested, 39 (78 percent) were B27 positive.[21]

In 1966 Noer reported nine cases of Reiter's syndrome among the crew of a United States Navy vessel in the Mediterranean, after Shigella dysentery had developed in 602 crew members (an incidence of 1.5 percent).[19] All nine were men. The syndrome began an average of 17 days after onset of the dysentery. All nine patients had polyarthritis, eight had urethritis and seven had conjunctivitis. The erythrocyte sedimentation rate was increased in all. Arthritis lasted an average of about two months, urethritis ten days and conjunctivitis five days. The knees and ankles were by far the most frequently involved joints. Recently Calin and Fries reported a follow-up study of five of Noer's patients.[22] All five had severe residual disease, including chronic arthritis, urethritis, ocular damage or spondylitis, or both, in most. One patient had blurred vision, and another was blind in one eye. Four of the five were B27 positive, corresponding to the high rates reported elsewhere. The authors calculated that about 35 persons in whom dysentery developed were probably B27 positive. Hence four to eight of 35, or 12 to 22 percent, of B27-positive persons were affected following an episode of dysentery.

In 1969 Davies and co-workers reported postdysenteric Reiter's syndrome in three male family members.[23] Like the present patient, they became afflicted after Shigella flexneri dysentery developed while on vacation in Mexico (Yucatan). Though familial involvement certainly suggests a genetic predisposition, tissue typing unfortunately was not done.

HLA-B27 has now been linked with a variety of illnesses associated with spondylitis, including Reiter's syndrome, ankylosing spondylitis, inflammatory bowel disease, psoriasis and Yersinia arthritis.[5,6,9] The manner in which it predisposes to these illnesses is unknown. It may be that linkage of B27 to a gene controlling the immune response to an infectious agent accounts for its association with spondylitis.[24] In patients with postdysenteric Reiter's syndrome, immunity to Shigella (or Salmonella) or its products might be different from that of patients with dysentery uncomplicated by Reiter's syndrome.

ADDENDUM: Another report of postdysenteric Reiter's syndrome has just appeared: Good AE, Schultz JS: Reiter's syndrome following Shigella flexneri 2a: A sequel to traveler's diarrhea. Arthritis Rheum 20:100-104, 1977.

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Refer to: Marlow AA, Evans ER: Chronic lymphocytic leukemia —First pathological signs after 22 years. West J Med 126:408-409, May 1977

Chronic Lymphocytic Leukemia

First Pathological Signs After 22 Years

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SINCE 1941 we have followed a patient with well-documented chronic lymphocytic leukemia but without physical signs of the disease being seen until 1963, other than an abnormal blood count first found in 1938.

The patient had been working as a missionary in Nagasaki, Japan. Four or five years before she was first seen in 1941, she began to tire easily and she felt the need of a furlough. She was retired and returned to Los Angeles, where, on August 30, 1938, a blood count showed a hemoglobin level of 13.17 grams per 100 ml; red blood cell count, 4,580,000 per cu mm; leukocyte count, 31,300 per cu mm; segmented neutrophils, 12 percent; basophils, 0.5 percent; lymphocytes, 86.5 percent; monocytes, 0.5 percent; myelocytes, 0.5 percent. The comment at the time read: "The lymphocytes showed monotony in size and shape and an occasional cell showed slight immaturity. No nucleated red cells found. Platelets appear normal in number."

At the age of 55 the patient moved to the San Diego area. When first seen there in January 1941 her only complaint was easy fatigability, which did not prevent her teaching part-time and taking care of her aging father. Her medical history included measles, mumps, whooping cough and chicken pox in childhood. Diphtheria occurred at the age of 12 with a history of a severe reaction to antitoxin. Anemia was described for 1½ years at the age of 18 and was said to have been corrected by a regimen of iron and beefsteak. The tonsils had been removed 15 years before and a prophylactic appendectomy had been done 10 years earlier. The patient's mother had had carcinoma of the stomach and had died of a stroke at the age of 73. There was no other family history of neoplasm or leukemia.

On a complete general physical examination, the patient was found to be well developed and well nourished, and appeared to be in good health at the age of 55. Temperature, pulse and respiration were normal. Blood pressure was 130/70. There was slight, diffuse enlargement of the thyroid gland without nodularity or signs of thyroid dysfunction. The remainder of the physical examination failed to disclose additional abnormalities.

The hemoglobin level was 13.4 grams per 100 ml; hematocrit reading, 41 percent; red blood cell count, 4,300,000 per cu mm, and leukocyte count, 43,500 per cu mm with segmented neutrophils, 15 percent; lymphocytes, 83 percent, and monocytes, 2 percent. Platelets appeared normal in number and no abnormalities of the red blood cells were recorded. Findings on analysis of urine were within normal limits.

Follow-up visits occurred at intervals of one to three months without important change noted for 22 years until September 1963, when we saw her in preparation for a move to a retirement home in Pasadena, California. Findings on physical examination were unchanged. The blood count was reported as follows: hemoglobin level, 11 grams per 100 ml; hematocrit reading, 37 percent, and leukocyte count, 63,500 per cu mm with band neutrophils, 1 percent; segmented neutrophils, 15 percent; lymphocytes, 82 percent; monocytes, 2 percent; platelets, 150,000 per cu mm; reticulocytes, 1.5 percent.

When she moved to Pasadena, one of us (E.R.E.) assumed the patient's care. At her first visit on April 1, 1963, a tiny supraclavicular node on the left was the only abnormal physical finding. Hemoglobin level was 12 grams per 100 ml; hematocrit reading 38 percent, and leukocyte count 56,000 per cu mm with band neutrophils, 12 percent; segmented neutrophils, 1 percent; lymphocytes, 86 percent; monocytes, 1 percent. By August 1965 tiny bilateral cervical nodes had developed. When the patient was seen in January 1969, the spleen was palpable 3 cm below the left costal margin and the liver 4 cm below the right costal margin. The cervical and right axillary nodes were enlarged 0.5 cm. By July 1971 the largest node measured 3 cm in diameter and

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the spleen size had increased to 9 cm below the left costal margin. The hemoglobin level was 11.7 grams per 100 ml; hematocrit reading 34 percent; leukocyte count, 50,000 per cu mm; band neutrophils, 1 percent; segmented neutrophils, 3 percent; lymphocytes, 95 percent, monocytes, 1 percent. Therapy with chlorambucil, 4 mg given orally each day, was started and was discontinued in September 1971, when the hemoglobin level was 11.4 grams per 100 ml; hematocrit reading, 33 percent; leukocyte count, 24,600 per cu mm; segmented neutrophils, 5 percent; lymphocytes, 94 percent; monocytes, 1 percent.

Chlorambucil was then given in daily oral doses of 4 mg (with one exception, when 2 mg was given) over periods of two or three months, with rest periods of several months between, until June 1975 when this therapy was discontinued (Table 1).

A lymphocyte surface immunoglobulin differential count in August 1974 showed a pronounced absolute, 71.5 percent type B lymphocytosis.

A protein electrophoresis in October 1974 showed total protein, 6.7 grams per 100 ml; albumin, 4 grams per 100 ml; alpha 1 globulin, 0.3 grams per 100 ml, and alpha 2 globulin, 0.7 grams per 100 ml; gamma globulin, 1.09 grams per 100 ml. Immunoglobulins on the same date were gamma A, 28 mg per 100 ml; gamma G, 500 mg per 100 ml; gamma M, 17 mg per 100 ml.

The sternal bone marrow showed considerable dilution with peripheral blood on Wright smears. An occasional megakaryocyte and normoblast were seen. At least 90 percent of the nucleated elements were mature lymphocytes. The remainder were myeloid cells and normoblasts.

The patient was last seen by one of us (E.R.E.) in September, 1975 at the age of 89. She had mild congestive heart failure. Posterior cervical, supraclavicular and axillary lymph nodes were enlarged to 1 cm in diameter. No other lymph nodes were palpable. The spleen and liver were enlarged to 5 cm below their respective costal margins. The hemoglobin was 12.4 grams per 100 ml; hematocrit reading, 36 percent, and leukocyte count, 6,000 per cu mm with 46 percent neutrophils; 52 percent lymphocytes and 2 percent monocytes. The platelet count was 190,000 per cu mm (Table 2).

TABLE 1.—*Chlorambucil Therapy*

Chlorambucil Dosage/Day		*Subtotal*
6-29-71	4 mg	
9-17-71	Discontinued	316
11-29-71	4 mg	
1-31-72	Discontinued	248
5- 3-72	4 mg	
8- 8-72	2 mg	384
9- 7-72	Discontinued	58
8-11-73	4 mg	
10-11-73	Discontinued	240
8-27-74	4 mg	
11-25-74	Discontinued	356
2-25-75	4 mg	
6-10-75	Discontinued	416
		Total dose 2,018 mg

TABLE 2.—*Representative Blood Counts*

Date	*Hemoglobin (gm percent)*	*Hematocrit (percent)*	*Leukocytes (cu mm)*	*Lymphocytes (percent)*
8-30-38	13.17	..	31,300	86.5
1-30-41	13.4	41	43,500	83
9-20-62	11	37	63,500	82
4- 1-63	12	38	56,000	86
7-27-72*	11.7	34	50,000	95
9-17-71†	11.4	33	24,600	94
9-11-75	12.4	36	6,000	52

*First course of chlorambucil 4 mg orally started.
†First course of chlorambucil discontinued.

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Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgment before publication.

Bypass, Boeing and Billions

TO THE EDITOR: The use of coronary bypass operations has blossomed into an industry of monumental proportions. It is estimated that in 1977 there will be 100,000 of these procedures done. They will be associated with a galaxy of subcontractors — exercise testing, angiography, cardiopulmonary units, heart-lung machines — and a host of physicians, technicians and nurses to go with them.

It is no wonder, therefore, that the cost of each procedure along with its satellite costs will be in the neighborhood of $12,000. And 100,000 times $12,000 means the coronary bypass industry will exceed one billion dollars in 1977 alone.

Yet, here we are ten years after the inception of the procedure and the data we have accumulated leave us only reasonably sure that it extends life in the restricted instance of disease of the left main coronary artery. There is growing evidence to support the contention that medical management in most other cases is at least as effective as surgical operation.

There is a flurry of interest in firming up the specifics for application of bypass surgical procedures and we can look forward to the elucidation of some further "reasonably certain" indications for it. These lessons will be of value and of interest, but they are not the most important lessons bypass should teach us.

First, we should ask ourselves a question: How could we let a billion-dollar industry develop in Medicine when we are so incredibly unsure of the product we have to sell? Surely outsiders—bureaucrats, insurers, the informed public—can hardly expect to remain sanguine about such reckless behavior by what now appears to be a permissive and irresponsible medical community.

We must learn that our behavior in this instance is unacceptable.

Let's look at another big industry and see how it behaves. When the directors of the Boeing aircraft company decide to make a jumbo jet they know they are committing their company to years of research and development. They also know that *only* when the product can fly and perform as promised will they be able to sell it. They don't fail to remember that the sale of a new product has not two but three requirements. Research and development of course, but in addition adequate, carefully controlled trial must precede any hope that the product will be accepted.

If the promoters of coronary bypass were making airplanes they would find it difficult to sell tickets on those planes with the paucity of adequate, carefully controlled trial which has been shown to date. In fact, medicine appears to belong in that part of the business world where Lockheed lurks—get something started and let cost-plus, no-limit public subsidies do the rest. It is as if a new medical procedure generates a special form of hysteria which pushes care and patience aside.

Even with all of its recent crop of warts, the Food and Drug Administration would not be expected to release a drug which could not prove its specific usefulness in the space of ten years.

The bypass procedure has been permitted to come to the public without a proper protocol and with little if any hint of licensure, certification, restriction or restraint upon it. It has been done in institutions where there is no possibility for the accumulation of significant, objective data about the procedure. As a result our current

opinions about bypass are based, after this long time, on only a fraction of the data which could be available.

Let's go back ten years and look at another scenario:

> The bypass procedure is developed. At that moment the medical profession institutes the restraint which will let the procedure get to the marketplace fully formed. It restricts application of the procedure to a dozen institutions which are fully capable of generating hard, objective data. (After all, we wouldn't expect Boeing to farm out its models to just any old wind tunnel.) Then, after five years—or ten, if need be—when the procedure and its areas of usefulness are fully understood, it is released to institutions for the general public application, along with a full set of instructions about when and where to apply it.

The above scenario, relieved of hysteria and opportunism, would permit this medical innovation to have a rational existence with no hint of the reckless abandon characterizing our present state of affairs.

Only if we change our manner of approach to new advances in medical care will we have an opportunity to direct traffic in the medical New World that is coming. And only a high degree of responsibility in these medical (and socioeconomic) areas will permit physicians a strong voice in the evolution of American health care.

Bypass has done some medical good. Now, if we have learned our lesson, it will have done much good for Medicine, as well.

DAVID L. RODGERS, MD
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A Complaint About Advertising

To the Editor: The road to hell is paved. Not only is it sleek concrete, but it has ten lanes, and the Federal Trade Commission (FTC) seems to have won the paving contract.

First the "good intentions" (that paved the road). In December 1975 the FTC filed a complaint against the American Medical Association, charging that its "principles of medical ethics" prohibited physicians from generating business by advertising, price competition and competitive practices. This resulted in a "restraint of trade." An FTC trial has been scheduled for September 1977. Implicit in the FTC complaint is a lack of homework at worst and an absence of reflection at best.

The purchase of medical services is a little different than comparison shopping for laundry soap. Our "product" is variable in ways unknown and often incomprehensible to potential consumers. Every physician could advertise and list his credentials: age, education, academic achievements, papers written, certification and so on. No question, this would be helpful to consumers who were sufficiently sophisticated to evaluate such *credentials,* but to the vast majority it would be meaningless. Also, a list of credentials for such purposes could easily mislead.

In the final essence, does it tell the potential patient that an individual physician so identified is a "good doctor"? Obviously it does not. Is the physician "worth" what he charges? (Even assuming he is able to predict in advance what the charge will be—which is impossible, since before the first encounter, the physician has no idea where the diagnostic and therapeutic trail will lead.) Even so, what is the price tag on competence, kindness, perserverance?

So most of us will not advertise. What do you put in an advertisement to "sell" your services (even if your waiting room were not overcrowded and you were beginning to book three to four months in advance). We will not advertise because we consider it unprofessional, impertinent and probably counterproductive to the health and welfare of our patients.

But there are some who revel in the infinite wisdom of the FTC—and do advertise. And they do it with all the elegant restraint of a carnival barker. A small but tawdry group of cosmetic surgeons offers swift success through cunning physical reconstruction, leading to a life of new and undreamed of delight and achievement.

The fat doctors and all the rest of the mangy pack of medical ridge runners—who have been swept under the rug of our conscience for so many years—are beginning to surface. They are bobbing up from the depth like red buoys, to taint us and taunt us with their unsavory exclamations. And this could be just the beginning. I can almost smell the snake oil and burning pine knots as a sophisticated 20th century medicine man, pulling out all the media stops, pushes (always in

subtle, carefully nonlitiginous language) his pitch —for treatment of all the disorders we cannot cure (cancer, low back pain, arthritides and the like).

It will be a field day for charlatans; a bleak day for physicians; a black day for patients.

I do not know what the solution is—for helping patients find "good doctors." The same could be said for good lawyers, good architects and good plumbers. Selecting an expert is always a chancy business, and advertising is not the answer. I suspect that like so many other things in this world, one must do it in the marketplace by trial and error. Admittedly in the case of medicine this is risky. What we have is far from ideal, but the alternatives are far worse.

Let us hope the FTC weighs all factors before further propagating this simplistic solution to a difficult problem.

ROBERT H. MOSER, MD
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Quality of Life

TO THE EDITOR: The quality of a physician's work is a reflection of the philosophy and ideas that motivate him. We have been told by great and noble men that reverence for life should be our guiding star. So we must ask the question, What is *life?* Is it a cell or group of cells carrying on the functions of respiration, digestion and excretion? Does it include bacteria, the prolific plankton of the seas, the hordes of insects that populate our planet, the rats and the mice that eat the farmers' grain, the fowl of the air and the beasts of the field? Do we worship at the throne of biology?

Nature has proven to be a wanton prodigal with much hatching and mitosing to permit the survival of a few samples of living things that in turn go about the business of reproduction in the endless cycle of living and dying. All of this activity is going on in a frenetic pattern often far below the level of awareness or intelligence. Is it really this physiologic activity that demands our allegiance and honor or is there something more important that demands our respect and obeisance? At what level of existence does life become meaningful and worthy of preservation? There is one product out of all this yeasty, budding, dividing and multiplying that demands reverence and enjoins our efforts at preservation. That product is intelligence—the ability to learn, evaluate, understand and love. Take it away and life is meaningless.

The real issue then is not whether we stepped on an ant, or swatted a fly, or ate a cow, but whether we ply our art or practice our trade or live our lives with intelligent compassionate understanding. Don't you agree, Dr. Schweitzer, wherever you are?

In our calling as physicians we are responsible to the human organism in a singular and peculiar way. We are concerned with the management of function of the biological machine. Like a mechanic with an oil-can and a wrench we tenderly grease and tighten the functioning parts, some physical, some psychic. We do not create intelligence nor do we assure quality to life. We service the machinery whereby man with his intelligence can find quality in life and for each man the quality goal may be different. To paraphrase an old bromide:

The physician says to man be free
Choose your life and what you will be
But this eternal truth is given
Life on earth is rarely Heaven
When vim and vigor become depleted
Doctor is in: Please be seated.

ORD L. SHUMWAY, MD
Hemet, California

Medicine Should Lead

TO THE EDITOR: THE WESTERN JOURNAL OF MEDICINE has an impressive record in addressing political, social and philosophical issues in the past few months.[1-4] I am very happy that the WESTERN JOURNAL has had the courage to address controversial areas. It is hard to see concrete change on the basis of editorializing. It is the more unfortunate because, as you have pointed out, physicians are still the most highly respected professionals in the United States. As a group, physicians are highly intelligent, articulate and well trained. Why, then, the irony that physicians are a weaker political force than, say, the Teamsters' union? Actually, it is fairly apparent. Training to be a physician leaves little time for political activity and even less for keeping up in the Arts. (It is a marvel that so many physicians manage to have outside talents, in spite of this.) Once through with training, now that a nonpolitical pattern has been established, physicians seldom get politically involved. Of course, a busy medical

practice makes it more difficult. Furthermore, physicians are individually fiercely independent. This makes it doubly difficult for anyone to lead a group of physicians. Consequently, less benevolent "interest groups" have more punch.

To change this it is first necessary to point out these facts and to realize the potential of Medicine as a leading force. Then it will be necessary to see the importance of exercising this potential in using medical expertise in directing our society. Finally, the process must start in medical school, where this potential and responsibility to society should be emphasized. The medical profession does have a responsibility to lead: to lead towards a cleaner, healthier environment; to lead towards personal responsibility in preventing self-inflicted disease (alcoholism, cigarette smoking, occupational disease). Part of health is mental health and part of mental health is happiness; Medicine should focus more on the social determinants of health and happiness.

Now is the time and the medical profession has the power and the responsibility to lead.

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Carcinogenicity of Fibrous Glass

To the Editor: There recently appeared in The Western Journal of Medicine [125:485, Dec 1976] a short scientific communication (epitome) by Jean Felton, MD, titled "Fiberglass—Not Carcinogenic." This note may do a disservice to the uninitiated in reporting this material as "biologically innocuous." This subject area should have been more critically reviewed.

The literature has numerous references attesting to the carcinogenicity of fibrous glass in experimental investigation. This has been established in a number of recent animal studies utilizing different routes of administration and fiber types. The work of Pott and Friedrichs (1974),[1] Stanton and Wrench (1972),[2] and Wagner, Berry and Skidmore (1974)[3] have demonstrated the ability of various forms of fibrous glass to induce malignant tumors in laboratory animals. Utilizing methods of surgical implantation, intraperitoneal and intrapleural inoculation of fibrous glass, tumors were developed in rats similar to those observed in asbestos-exposed animals and man.

These investigations are of importance because these materials are being increasingly used, particularly as a substitute for asbestos. There is also increasing use of narrow diameter (.05-3μm) fibers for thermal insulation and other products. These fibers are eminently respirable, durable and may represent the physical structure found most carcinogenic in animal experiments (Stanton 1974).[5,6] The assertion that contemporary work substantiates the classification of this material as inert is unsupported.[7-11] Questions of carcinogenicity of fibrous glass are unresolved and are, indeed, under very active study at this time (International Agency for Research Against Cancer, for example). This is largely due to the recent introduction of long, narrow fibers into the workplace and environment. Both fiber-induced fibrosis and carcinogenicity require long latent periods; for example, for mesothelioma usually more than 30 years. Epidemiological studies to date have had methodologic shortcomings and have dealt with workers exposed to thicker and therefore less respirable fibers.

We are concerned that fine fibrous glass fibers may be inhaled, migrate to the pleura and exert a carcinogenic effect in man exactly like asbestos and that fibrous glass may act as a lung co-carcinogen with cigarette smoke and other carcinogens. We are not convinced that fibrous glass does not have a cellular toxic effect on alveolar macrophages and pulmonary living cells that may lead to fibrosis.

That fibrous glass may be biologically hazardous if inhaled into the lung is a potentially important problem which deserves extensive and urgent study.

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The Panel Responds

To the Editor: The comments of Drs. Rom and Langer are appreciated and valued; they come from an investigative group long identified with significant contributions in the field of fibrogenic pulmonary disease.

The epitome encapsulated the opinions of Milne and Gross whose writings have appeared in scholarly, peer-review journals. In essence, the implantation studies cited embodied artificial introductions of fibers into the pleural cavity, and in quantities in excess of those possible in occupational exposure. Further, extrapolation of findings from one species to another may produce fallacious conclusions.

To be sure, direct deposition of fibers provoked tumors, but replication *in vivo* in the intact thorax bears no immediate relationship to the reality of the work setting.

It is agreed that long latent periods are needed for carcinogenicity in asbestos exposure, and glass fiber should be pursued as a comparable toxic agent under the circumstances of worker contact and inhalation.

J. S. FELTON, MD
Current Chairman, CMA
Industrial Medicine Advisory Panel
Long Beach

Tracking Down Migraine

Patients have a built-in aversion to the word "migraine." They will not use that term; they don't like it . . . . I ask them this: "Are you headachy?" Don't ask a patient "Do you have headaches?" He'll tell you about the time he got hit on the head at a football game in 1937 . . . . How do you get that family history? That is very important. If you say "Did your mother or dad ever have migraine?" "No!" That's what they'll say right off the bat. Don't ask them that. Ask them this: "Did your mother or dad have sick headaches?" "No." They may even hold on that. "Well, was your mother or dad headachy?" "Oh, yes! My dad had bad headaches. But he had sinus headaches." They'll call it sinus headache, they'll call it hypertensive headache, they'll call it allergic headache and they'll call it tension headache. If you go into the history, it's migraine time after time after time. The family history is critical. So you can't say "Did they have headaches?" You've got to say "Were they headachy?"

—J. LAWTON SMITH, MD, *Miami*
Extracted from *Audio-Digest Ophthalmology*, Vol. 14, No. 11, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1577 East Chevy Chase Drive, Glendale, CA 91206.

Refer to: Cohen SN: Recombinant DNA: Fact and fiction (Reprinted from Science 195:654-657, Feb 18, 1977). West J Med 126:415-420, May 1977

Special Article

Recombinant DNA: Fact and Fiction

STANLEY N. COHEN, MD, *Stanford*

ALMOST THREE YEARS AGO, I joined with a group of scientific colleagues in publicly calling attention to possible biohazards of certain kinds of experiments that could be carried out with newly developed techniques for the propagation of genes from diverse sources in bacteria.[1] Because of the newness and relative simplicity of these techniques,[2,3] we were concerned that experiments involving certain genetic combinations that seemed to us to be hazardous might be performed before adequate consideration had been given to the potential dangers. Contrary to what was believed by many observers, our concerns pertained to a few very specific types of experiments that could be carried out with the new techniques, not to the techniques themselves.

Guidelines have long been available to protect laboratory workers and the general public against known hazards associated with the handling of certain chemicals, radioisotopes and pathogenic microorganisms; but because of the newness of recombinant DNA (deoxyribonucleic acid) techniques, no guidelines were yet available for this research. My colleagues and I wanted to be sure that these new techniques would not be used, for example, for the construction of streptococci or pneumococci resistant to penicillin, or for the creation of Escherichia coli capable of synthesizing botulinum toxin or diphtheria toxin. We asked that these experiments not be done, and also called for deferral of construction of bacterial recombinants containing tumor virus genes until the implications of such experiments could be given further consideration.

During the past two years, much fiction has been written about "recombinant DNA research." What began as an act of responsibility by scientists, including a number of those involved in the development of the new techniques, has become the breeding ground for a horde of publicists—most poorly informed, some well-meaning, some self-serving. In this article I attempt to inject some relevant facts into the extensive public discussion of recombinant DNA research.

Some Basic Information

Recombinant DNA research is not a single entity, but rather it is a group of techniques that can be used for a wide variety of experiments. Much confusion has resulted from a lack of understanding of this point by many who have written about the subject. Recombinant DNA techniques, like chemicals on a shelf, are neither good nor bad per se. Certain experiments that can be done with these techniques are likely to be hazardous (just as certain experiments done with combinations of chemicals taken from the shelf will be hazardous), and there is universal agreement that such recombinant DNA experiments should not be done. Other experiments in which the very same techniques are used—such as taking apart a DNA molecule and putting segments of it back together again—are without conceivable hazard, and anyone who has looked into the matter has concluded that these experiments can be done without concern.

Then, there is the area "in between." For many experiments, there is no evidence of biohazard,

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This article is adapted from a statement prepared for a meeting of the California Medical Association Committee on Environmental Health held November 18, 1976; and is reprinted, with permission of the author and publisher, from Science 195:654-657, Feb 18, 1977; Copyright 1977 by the American Association for the Advancement of Science.

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but there is also no certainty that there is not a hazard. For these experiments, guidelines have been developed in an attempt to match a level of containment with a degree of hypothetical risk. Perhaps the single point that has been most misunderstood in the controversy about recombinant DNA research is that discussion of "risk" in the middle category of experiments relates entirely to hypothetical and speculative possibilities, not expected consequences or even phenomena that seem likely to occur on the basis of what is known. Unfortunately, much of the speculation has been interpreted as fact.

There is nothing novel about the principle of matching a level of containment with the level of anticipated hazard; the containment procedures used for pathogenic bacteria, toxic substances and radioisotopes attempt to do this. However, the containment measures used in these areas address themselves only to known hazards and do not attempt to protect against the unknown. If the same principle of protecting only against known or expected hazards were followed in recombinant DNA research, there would be no containment whatsoever except for a very few experiments. In this instance, we are asking not only that there be no evidence of hazard, but that there be positive evidence that there is no hazard. In developing guidelines for recombinant DNA research, we have attempted to take precautionary steps to protect ourselves against hazards that are not known to exist—and this unprecedented act of caution is so novel that it has been widely misinterpreted as implying the imminence or at least the likelihood of danger.

Much has been made of the fact that, even if a particular recombinant DNA molecule shows no evidence of being hazardous at the present time, we are unable to say for certain that it will not prove to be harmful some years hence. Of course this view is correct; similarly, we are unable to say for certain that the vaccines we are administering to millions of children do not contain agents that will produce contagious cancer some years hence, we are unable to say for certain that a virulent virus will not be brought to the United States next winter by a traveler from abroad, causing a nationwide fatal epidemic of a hitherto unknown disease—and we are unable to say for certain that novel hybrid plants being bred around the world will not suddenly become weeds that will overcome our major food crops and cause worldwide famine.

The statement that potential hazards could result from certain experiments involving recombinant DNA techniques is akin to the statement that a vaccine injected today into millions of people *could* lead to infectious cancer in 20 years, a pandemic caused by a traveler-borne virus *could* devastate the United States or a new plant species *could* uncontrollably destroy the world's food supply. We have no reason to expect that any of these things will happen, but we are unable to say for certain that they will not happen. Similarly, we are unable to guarantee that any of man's efforts to influence the earth's weather, explore space, modify crops or cure disease will not carry with them the seeds for the ultimate destruction of civilization. Can we in fact point to one major area of human activity where one can say *for certain* that there is no risk? Potentially, we could respond to such risks by taking measures such as prohibiting foreign travel to reduce the hazard of deadly virus importation and stopping experimentation with hybrid plants. It is possible to develop plausible "scare scenarios" involving virtually any activity or process, and these would have as much (or as little) basis in fact as most of the scenarios involving recombinant DNA. But we must distinguish fear of the unknown from fear that has some basis in fact; this appears to be the crux of the controversy surrounding recombinant DNA.

Unfortunately, the public has been led to believe that the biohazards described in various scenarios are likely or probable outcomes of recombinant DNA research. "If the scientists themselves are concerned enough to raise the issue," goes the fiction, "the problem is probably much worse than anyone will admit." However, the simple fact is that there is no evidence that a bacterium carrying any recombinant DNA molecule poses a hazard beyond the hazard that can be anticipated from the known properties of the components of the recombinant. And experiments involving genes that produce toxic substances or pose other known hazards are prohibited.

Freedom of Scientific Inquiry

This issue has been raised repeatedly during discussions of recombinant DNA research. "The time has come," the critics charge, "for scientists to abandon their long-held belief that they should be free to pursue the acquisition of new knowledge regardless of the consequences." The fact is that

no one has proposed that freedom of inquiry should extend to scientific experiments that endanger public safety. Yet, "freedom of scientific inquiry" is repeatedly raised as a straw-man issue by critics who imply that somewhere there are those who argue that there should be no restraint whatsoever on research.

Instead, the history of this issue is one of self-imposed restraint by scientists from the very start. The scientific group that first raised the question of possible hazard in some kinds of recombinant DNA experiments included most of the scientists involved in the development of the techniques—and their concern was made public so that other investigators who might not have adequately considered the possibility of hazard could exercise appropriate restraint. While most scientists would defend their right to freedom of scientific thought and discourse, I do not know of anyone who has proposed that scientists should be free to do whatever experiments they choose regardless of the consequences.

Interference with "Evolutionary Wisdom"

Some critics of recombinant DNA research ask us to believe that the process of evolution of plants, animals and microbes has remained delicately controlled for millions of years, and that the construction of recombinant DNA molecules now threatens the master plan of evolution. Such thinking, which requires a belief that nature is endowed with wisdom, intent and foresight, is alien to most post-Darwinian biologists.* Moreover, there is no evidence that the evolutionary process is delicately controlled by nature. To the contrary, man has long ago modified the process of evolution, and biological evolution continues to be influenced by man. Primitive man's domestication of animals and cultivation of crops provided an "unnatural" advantage to certain biological species and a consequent perturbation of evolution. The later creation by man of hybrid plants and animals has resulted in the propagation of new genetic combinations that are not the products of natural evolution. In the microbiological world, the use of antimicrobial agents to treat bacterial infections and the advent of mass immunization programs against viral disease has made untenable the thesis of delicate evolutionary control.

A recent letter[4] that has been widely quoted by critics of recombinant DNA research asks, "Have we the right to counteract irreversibly the evolutionary wisdom of millions of years . . . ?" It is this so-called evolutionary wisdom that gave us the gene combinations for bubonic plague, smallpox, yellow fever, typhoid, polio, diabetes and cancer. It is this wisdom that continues to give us uncontrollable diseases such as Lassa fever, Marburg virus, and very recently the Marburg-related hemorrhagic fever virus, which has resulted in nearly 100 percent mortality in infected individuals in Zaire and the Sudan. The acquisition and use of all biological and medical knowledge constitutes an intentional and continuing assault on evolutionary wisdom. Is this the "warfare against nature" that some critics fear from recombinant DNA?

How About the Benefits?

For all but a very few experiments, the risks of recombinant DNA research are speculative. Are the benefits equally speculative or is there some factual basis for expecting that benefits will occur from this technique? I believe that the anticipation of benefits has a substantial basis in fact, and that the benefits fall into two principal categories: (1) advancement of fundamental scientific and medical knowledge and (2) possible practical applications.

In the short space of 3½ years, the use of the recombinant DNA technology has already been of major importance in the advancement of fundamental knowledge. We need to understand the structure and function of genes, and this methodology provides a way to isolate large quantities of specific segments of DNA in pure form. For example, recombinant DNA methodology has provided us with much information about the structure of plasmids that cause antibiotic resistance in bacteria, and has given us insights into how these elements propagate themselves, how they evolve, and how their genes are regulated. In the past, our inability to isolate specific genetic regions of the chromosomes of higher organisms has limited our understanding of the genes of complex cells. Now use of recombinant DNA techniques has provided knowledge about how genes are organized into chromosomes and how gene expression is con-

*If we accept the view that any natural barriers to the propagation of genetic material derived from unrelated species do not owe their existence to the intent of nature, we can reason that evolution has created and maintained such barriers because opportunities for genetic mixing occur in nature. Furthermore, we must conclude that limitations to gene exchange have evolved because the mixing of genes from diverse organisms is biologically undesirable—not in a moral or theological sense as some observers would have us believe—but to those organisms involved.

trolled. With such knowledge we can begin to learn how defects in the structure of such genes alter their function.

On a more practical level, recombinant DNA techniques potentially permit the construction of bacterial strains that can produce biologically important substances such as antibodies and hormones. Although the full expression of higher organism DNA that is necessary to accomplish such production has not yet been achieved in bacteria, the steps that need to be taken to reach this goal are defined, and we can reasonably expect that the introduction of appropriate "start" and "stop" control signals into recombinant DNA molecules will enable the expression of animal cell genes. On an even shorter time scale, we can expect recombinant DNA techniques to revolutionize the production of antibiotics, vitamins, and medically and industrially useful chemicals by eliminating the need to grow and process the often exotic bacterial and fungal strains currently used as sources for such agents. We can anticipate the construction of modified antimicrobial agents that are not destroyed by the antibiotic inactivating enzymes responsible for drug resistance in bacteria.

In the area of vaccine production, we can anticipate the construction of specific bacterial strains able to produce desired antigenic products, eliminating the present need for immunization with killed or attenuated specimens of disease-causing viruses.

One practical application of recombinant DNA technology in the area of vaccine production is already close to being realized. An E. coli plasmid coding for an enteric toxin fatal to livestock has been taken apart, and the toxin gene has been separated from the remainder of the plasmid. The next step is to cut away a small segment of the toxin-producing gene so that the substance produced by the resulting gene in E. coli will not have toxic properties but will be immunologically active in stimulating antibody production.

Other benefits from recombinant DNA research in the areas of food and energy production are more speculative. However, even in these areas there is a scientific basis for expecting that the benefits will someday be realized. The limited availability of fertilizers and the potential hazards associated with excessive use of nitrogen fertilizers now limits the yields of grain and other crops, but agricultural experts suggest that transplantation of the nitrogenase system from the chromosomes of certain bacteria into plants or into other bacteria that live symbiotically with food crop plants may eliminate the need for fertilizers. For many years, scientists have modified the heredity of plants by comparatively primitive techniques. Now there is a means of doing this with greater precision than has been possible previously.

Certain algae are known to produce hydrogen from water, using sunlight as energy. This process potentially can yield a virtually limitless source of pollution-free energy if technical and biochemical problems indigenous to the known hydrogen-producing organisms can be solved. Recombinant DNA techniques offer a possible means of solution to these problems.

It is ironic that some of the most vocal opposition to recombinant DNA research has come from those most concerned about the environment. The ability to manipulate microbial genes offers the promise of more effective utilization of renewable resources for mankind's food and energy needs; the status quo offers the prospect of progressive and continuing devastation of the environment. Yet, some environmentalists have been misled into taking what I believe to be an antienvironmental position on the issue of recombinant DNA.

The NIH Guidelines

Even if hazards are speculative and the potential benefits are significant and convincing, wouldn't it still be better to carry out recombinant DNA experiments under conditions that provide an added measure of safety—just in case some of the conjectural hazards prove to be real?

This is exactly what is required under the NIH (National Institutes of Health) guidelines[5] for recombinant DNA research:

1. These guidelines prohibit experiments in which there is some scientific basis for anticipating that a hazard will occur. In addition, they prohibit experiments in which a hazard, although it might be entirely speculative, was judged by NIH to be potentially serious enough to warrant prohibition of the experiment. The types of experiment that were the basis of the initial "moratorium" are included in this category; contrary to the statements of some who have written about recombinant DNA research, there has in fact been no lifting of the original restrictions on such experiments.

2. The NIH guidelines require that a large class of other experiments be carried out in P4 (high level) containment facilities of the type designed

for work with the most hazardous naturally occurring microorganisms known to man (such as Lassa fever virus, Marburg virus and Zaire hemorrhagic fever virus). It is difficult to imagine more hazardous self-propagating biological agents than such viruses, some of which lead to nearly 100 percent mortality in infected individuals. The P4 containment requires a specially built laboratory with airlocks and filters, biological safety cabinets, clothing changes for personnel, autoclaves within the facility and the like. This level of containment is required for recombinant DNA experiments for which there is at present no evidence of hazard, but for which it is perceived that the hazard might be potentially serious if conjectural fears prove to be real. There are at present only four or five installations in the United States where P4 experiments could be carried out.

3. Experiments associated with a still lesser degree of hypothetical risk can be conducted in P3 containment facilities. These are also specially constructed laboratories requiring double door entrances, negative air pressure and special air filtration devices. Facilities where P3 experiments can be performed are limited in number, but they exist at some universities.

4. Experiments in which the hazard is considered unlikely to be serious even if it occurs still require laboratory procedures (P2 containment) that have for years been considered sufficient for research with such pathogenic bacteria as Salmonella typhosa, Clostridium botulinum, and Cholera vibrio. The NIH guidelines require that P2 facilities be used for work with bacteria carrying interspecies recombinant DNA molecules that have shown no evidence of being hazardous—and even for some recombinant DNA experiments in which there is substantial evidence of lack of hazard.

5. The P1 (lowest) level of containment can be used only for recombinant DNA molecules that potentially can be made by ordinary biological gene exchange in bacteria. Conformity to even this lowest level of containment in the laboratory requires decontamination of work surfaces daily and after spills of biological materials, the use of mechanical pipetting devices or cotton plugged pipettes by workers, a pest control program, and decontamination of liquid and solid waste leaving the laboratory.

In other areas of actual or potential biological hazard, physical containment is all that microbiologists have had to rely upon; if the Lassa fever virus were to be released inadvertently from a P4 facility, there would be no further barrier to prevent the propagation of this virus, which is known to be deadly and for which no specific therapy exists. However, the NIH guidelines for recombinant DNA research have provided for an additional level of safety for workers and the public: This is a system of biological containment that is designed to reduce by many orders of magnitude the chance of propagation outside the laboratory of microorganisms used as hosts for recombinant DNA molecules.

An inevitable consequence of these containment procedures is that they have made it difficult for the public to appreciate that most of the hazards under discussion are conjectural. Because in the past, governmental agencies have often been slow to respond to clear and definite dangers in other areas of technology, it has been inconceivable to scientists working in other fields and to the public at large that an extensive and costly federal machinery would have been established to provide protection in this area of research unless severe hazards were known to exist. The fact that recombinant DNA research has prompted international meetings, extensive coverage in the news media and governmental intervention at the federal level has been perceived by the public as prima facie evidence that this research must be more dangerous than all the rest. The scientific community's response has been to establish increasingly elaborate procedures to police itself—but these very acts of scientific caution and responsibility have only served to perpetuate and strengthen the general belief that the hazards under discussion must be clear-cut and imminent in order for such steps to be necessary.

It is worth pointing out that despite predictions of imminent disaster from recombinant DNA experiments, the fact remains that during the past 3½ years, many billions of bacteria containing a wide variety of recombinant DNA molecules have been grown and propagated in the United States and abroad, incorporating DNA from viruses, protozoa, insects, sea urchins, frogs, yeast, mammals and unrelated bacterial species into E. coli, without hazardous consequences so far as I am aware. And the majority of these experiments were carried out prior to the strict containment procedures specified in the current federal guidelines.

Despite the experience thus far, it will always be valid to argue that recombinant DNA molecules that seem safe today may prove hazardous to-

morrow. One can no more prove the safety of a particular genetic combination under all imaginable circumstances than one can prove the currently administered vaccines do not contain an undetected self-propagating agent capable of producing cancer in the future, or that a hybrid plant created today will not lead to disastrous consequences some years hence. No matter what evidence is collected to document the safety of a new therapeutic agent, a vaccine, a process or a particular kind of recombinant DNA molecule, one can always conjure up the possibility of future hazards that cannot be disproved. When one deals with conjecture, the number of possible hazards is unlimited; the experiments that can be done to establish the absence of hazard are finite in number.

Those who argue that we should not use recombinant DNA techniques until or unless we are absolutely certain that there is zero risk fail to recognize that no one will ever be able to guarantee total freedom from risk in any significant human activity. All that we can reasonably expect is a mechanism for dealing responsibly with hazards that are known to exist or which appear likely on the basis of information that is known. Beyond this, we can and should exercise caution in any activity that carries us into previously uncharted territory, whether it is recombinant DNA research, creation of a new drug or vaccine or bringing a spaceship back to Earth from the moon.

Today, as in the past, there are those who would like to think that there is freedom from risk in the status quo. However, even the status quo presents unknown risks, as well as a large collection of known hazards. Humanity continues to be buffeted by ancient and new diseases, and by malnutrition and pollution; recombinant DNA techniques offer a reasonable expectation for a partial solution to some of these problems. Thus, we must ask whether we can afford to allow preoccupation with and conjecture about hazards that are not known to exist, to limit our ability to deal with hazards that do exist. Is there in fact greater risk in proceeding judiciously, or in not proceeding at all? We must ask whether there is any rational basis for predicting the dire consequences of recombinant DNA research portrayed in the scenarios proposed by some. We must then examine the benefit side of the picture and weigh the already realized benefits and the reasonable expectation of additional benefits, against the vague fear of the unknown that has in my opinion been the focal point of this controversy.

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Trauma Rounds

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Initial Evaluation and Treatment of Multiply-Injured Patients

DAVID TAPPER, MD:* The case for presentation today involves a 27-year-old woman who was admitted to the emergency room apparently having just been hit by a car while crossing the street.

On examination at admission, the patient was comatose with a blood pressure of 90/60 mm of mercury and a thready pulse rate of 120 beats per minute. The extremities were cool and the neck veins flat. Mid-dilatation of the pupils was noted; there was an abrasion and hematoma of the right parietal area and a left supraorbital laceration. There was a laceration of the chin 3 cm long.

Respiration was rapid and shallow. There were palpable fractures in the left posterior part of the chest involving ribs 8 through 10. Breath sounds were present bilaterally. The abdomen was scaphoid and firm with no masses palpable.

On examination of the extremities, a deformity of the left leg was seen compatible with a midshaft fracture of both bones and a 3 to 4 cm laceration over the mid portion of the tibia. Pulses were present in both feet.

F. WILLIAM BLAISDELL, MD:† I have asked Dr. Carleton Mathewson to lead a panel discussion today because our trauma unit at San Francisco General Hospital is being dedicated today in his honor. On the basis of his long interest in trauma, I have selected for the discussion one of his favorite subjects, the management of multiply-injured patients.

CARLETON MATHEWSON, MD:‡ The patient just presented represents an example of the basic difficulty that a multiply-injured patient poses. This consists of identification of the problems, development of priorities for their management and the administration of definitive treatment. The management in this case starts with a question: who is in charge? There is no doubt that the person who assumes responsibility for this type of patient should be the best qualified surgeon or surgical specialist available whose perspective is able to encompass the patient as a whole. In most instances, this means a general surgeon with a special interest in traumatology.

Unfortunately, in many hospitals the management of trauma is relegated to the most junior surgeons on the staff who, because of their availability, assume responsibility for such cases. The more senior surgeon who has acquired the most experience in making sound clinical judgments may have been successful enough to have opted out of emergency work altogether. The staff at San Francisco General Hospital is unusual in that

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it assembles a group of dedicated specialists with specific interest in trauma.

I would like to select from our panel today a general surgeon, Dr. Muriel Steele. How would you proceed with this patient, assuming you were in charge?

MURIEL STEELE, MD:* The patient presents with the standard problems of a multiply-injured patient. We would proceed (as assumed in the case presentation) with a rapid, complete examination of the patient. This usually can be carried out in 30 to 60 seconds; at most it requires a minute or two. Because this patient is comatose with evidence of head trauma, the possibility of cervical fracture exists and should be assumed. We would roll the patient on her side and do an immediate examination of the back, keeping the head and neck in a neutral position by supporting the head at the angle of the jaw.

After quick assessment, the injuries are noted and a diagnostic and therapeutic plan is developed based on the urgency of each problem. The airway assumes priority. If the patient has no vital reflexes (gag, cough or swallowing), the airway must be protected from aspiration by the immediate insertion of an endotracheal tube. If there is evidence of respiratory distress due to chest trauma as was manifested here, regardless of the state of consciousness, resuscitation would require endotracheal intubation as well. In addition, one should assess what is going on in the pleural cavity. In this case I would favor the placement of a large bore tube in the left side of the chest, which would permit the identification of pneumothorax and assessment of intrapleural bleeding.

Next in priority comes support of the cardiovascular system. In this case, the combination of low blood pressure, poor peripheral perfusion and collapsed neck veins is indicative of hypovolemic shock. Management requires gaining immediate access to the cardiovascular system by the insertion of catheters to accessible veins and the immediate infusion of fluids to restore vascular volume. I would advise simultaneous cutdowns on two veins—one in the upper and one in the lower extremity. The arm vein selected is usually the antecubital vein, through which a long catheter such as an infant feeding tube can be passed up the basilic into a central vein. This permits fluid infusion or monitoring of central venous pressure.

The saphenous vein at the ankle is the most accessible large vein in the body and, when a patient presents in shock a short time after injury, massive blood loss can be assumed so that rapid administration of large volumes of fluid is mandatory. This vein accommodates the entire cross section of intravenous tubing and permits 1 to 2 liters of Ringer's lactate to be pushed in easily over a five to ten minute interval. When this is done, circulatory resuscitation is possible in all but massive vascular injury cases and time is granted for more definitive evaluation. If the blood pressure comes up transiently and then falls again, or does not respond at all, immediate operation is mandatory to control continuing hemorrhage.

I would like to add that the monitoring of urinary output is important and a urethral catheter should be placed as part of initial resuscitation whenever shock is identified. If fluid therapy results in a urinary output of 0.5 ml per kg of body weight or more per hour, then vital organ perfusion can be assumed to be adequate and time is available for more sophisticated evaluation. But if the urinary output does not respond to fluid administration, inadequate shock resuscitation is presumed. This is an indication for immediate operation to control bleeding.

DR. MATHEWSON: *What about the trauma and presumed head injury in this patient? Is it possible that the shock in this patient is neurogenically mediated?*

DR. STEELE: That is an unacceptable assumption. The poor peripheral perfusion and collapsed neck veins indicate shock and volume loss until proven otherwise. Lack of brain perfusion may account for coma, and restoration of circulation and control of bleeding is essential.

DR. MATHEWSON: *Dr. Pitts, as a neurosurgeon, would you agree?*

LAWRENCE PITTS, MD:† I most certainly would. We have learned that it is impossible to venture a prognosis in cases such as this, and only after circulation has been restored can complete, adequate neurosurgical evaluation be carried out. I might add, however, that after the airway and

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cardiovascular system, we believe the central nervous system comes next in priority, so that we appreciate seeing a patient such as this one in the emergency room before the induction of anesthesia. Then we can look for localizing signs and can carry out a neurologic examination which may provide a great deal of baseline information.

DR. MATHEWSON: *Dr. Steele was quite ready to place a chest tube in this patient. Dr. Thomas, would you agree with the method of procedure, and if so, why?*

ARTHUR THOMAS, MD:* In this patient there was evidence of thoracic injury as shown by palpable rib fractures on the left. She was in shock and we would like to be sure it is not due to tension pneumothorax or to massive hemorrhage into the pleural cavity. Certainly if the patient were stable and time permitted, we would prefer to have an x-ray study of the chest done to definitely determine the need for tube thoracotomy. In this patient, however, there appear to be multiple problems, so it would be preferable to assess the chest as rapidly as possible in order to stabilize this particular problem. In addition, if anesthesia is to be administered for laparotomy or support begun with positive pressure ventilation, a small laceration of the lung can be converted into a lethal problem. When air is pushed in the upper airway under increased atmospheric pressure, there is risk of producing tension pneumothorax if a lung laceration is present.

A chest tube can be placed quickly and monitoring of one or both pleural cavities obtained immediately. I prefer to place a large bore chest tube between 30 and 40 F of the Argile-type. The optimal location is between the 3rd and 6th interspace somewhere between the anterior and midaxillary line. This will decompress the pneumothorax and permit monitoring of the rate of blood loss in the chest. The absence of significant pleural blood loss or tension pneumothorax points to the abdomen as the presumed source of hemorrhage. I would agree with Dr. Steele entirely about the proposed management in this patient.

DR. MATHEWSON: *Dr. Tapper, would you tell us what was done?*

DR. TAPPER: The initial treatment consisted of splinting of the head and neck. The Anesthesia Service placed an orotracheal tube while cutdowns were being done on the right arm and ankle and intravenous lines inserted. A large bore tube was placed in the left pleural space and no blood or air was removed. A urethral catheter was placed and bloody fluid obtained. Two liters of Ringer's lactate were administered rapidly through the cutdowns over ten minutes shortly after arrival of the patient in the emergency room. Blood was drawn for hematocrit determination and typing.

With the administration of fluid, the pulse became stronger and the blood pressure rose to 100/50 mm of mercury. The patient seemed to move the left leg and right arm and leg, but not the left arm, which remained flail.

DR. MATHEWSON: *Dr. Steele, the abdomen in this case was described as benign. What would your next approach be?*

DR. STEELE: I would agree with the management so far. I would also presume, with the minimal return from the chest tube, that the problem lay in the abdomen. I would move this patient as rapidly toward the operating room as I could and would have x-ray films made en route. The lack of abdominal findings means nothing. If no source of blood loss is apparent clinically, the source most likely lies in the abdomen and exploratory laparotomy is indicated.

DR. MATHEWSON: *Dr. Thomas, would you agree?*

DR. THOMAS: Yes. An x-ray film of the chest, cervical and skull films, and a kidney, ureter and bladder study (KUB) should be obtained. For injuries such as this in which there may be urinary tract damage, approximately 50 to 100 ml of a contrast agent such as Renografin®-60 is given in the emergency room. When the KUB is taken subsequently, we will have information regarding the status of both kidneys.

DR. MATHEWSON: *Dr. Tapper, what was done?*

DR. TAPPER: Films of head and neck, chest, abdomen and pelvis were obtained 20 minutes after admission. Renografin-60 had been administered intravenously before transfer to radiology. No x-ray film of the leg was done. During administration of the third liter of Ringer's lactate in the x-ray room, the blood pressure fell to 60 systolic, the x-ray examination was discontinued and the patient taken to the operating room.

Laparotomy was carried out 35 minutes following admission. Two liters of blood was present

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in the peritoneal cavity. There was gross rupture of the spleen and a large left flank hematoma through which a transverse laceration of the kidney could be felt. There was a stellate laceration of the left lobe of the liver which was bleeding briskly. Burr holes were carried out simultaneously by the neurosurgeons.

DR. MATHEWSON: *Dr. Pitts, would you explain the reason for carrying out burr holes simultaneous with laparotomy? I thought you stated that neurologic damage could not be evaluated in the presence of hemorrhage and that you would defer to the general surgeon.*

DR. PITTS: In this instance, we felt that the development of localizing signs with persistent coma, despite the improvement of the cardiovascular status with the administration of Ringer's lactate, suggested the probability of cerebral injury. We would have liked to have done angiographic evaluation before taking the patient to the operating room, but the patient's unstable condition did not permit exercising that option. Since laparotomy was felt to be indicated by the general surgeons, and this undoubtedly would occupy considerable time, we felt that burr holes were indicated in order to rule out any immediately treatable neurosurgical processes such as subdural or epidural bleeding.

Six burr holes were placed, one in each frontal, parietal and temporal area. Contused, ecchymotic brain was noted on the right side but the brain was only under moderate tension and did not tend to herniate from the burr holes. We felt that the next procedure indicated was that of arteriography if the patient's general condition could be stabilized by the general surgeons and so advised them at the operating table.

DR. MATHEWSON: *Dr. Steele, how should the laparotomy proceed and how would you manage the injuries described?*

DR. STEELE: I would carry out the laparotomy utilizing a midline incision and as soon as blood was encountered, I would extend this incision from xiphoid nearly to pubis in order to obtain adequate exposure of the abdominal cavity. The patient would be eviscerated and the abdomen rapidly evaluated with inspection of all corners and then packing of each area while I moved to the next. Any area of hemorrhage would require immediate tamponade with appropriate pressure and laparotomy pads. After assessing the splenic and liver injury, I would have packed the left upper quadrant to be sure that there were no major bleeding points located elsewhere. Having ascertained that the probable source of most of the hemorrhage in the peritoneal cavity was the liver or spleen (or both), I would have returned to that area and carried out a splenectomy followed by control of the liver injury. I would palpate the retroperitoneal hematoma but would not necessarily open it unless it were expanding. I would also like to know what was seen on the x-ray studies, particularly on the intravenous pyelogram.

DR. TAPPER: The x-ray studies showed no cervical or skull fractures. The chest was clear, the KUB was not remarkable, there was good renal function on the right; the kidney could be seen on the left but the detail was poor. There was no evidence of gross extravasation of urine.

The liver laceration was packed and splenectomy carried out. Blood loss from the liver was then controlled by direct suture of several arterial bleeding points. The retroperitoneal hematoma was not opened but the lesser sac was inspected and the body and tail of the pancreas exposed. This organ was intact and there was no hematoma around the head of the pancreas or in the mesentery. After examining the bowel in its entirety and the remaining contents of the abdomen, the 12th rib was resected and a three-finger-breadth drain site developed. Penrose drains were placed around the area of liver injury and brought out from this left flank drainage site. All incisions were closed and the patient was taken to the x-ray room for cerebral and renal arteriograms. X-ray studies of the leg were also carried out. This examination occupied the next three hours. The patient was unstable in the x-ray room and 6 units of blood were required to maintain pressure. Findings on the cerebral arteriograms were not remarkable. On x-ray films of the kidney a complete fracture of the mid-portion of the left kidney was seen.

The films of the leg showed a comminuted fracture of the tibia and fibula. The abdomen had expanded during this period so that following completion of the x-rays the patient was taken back to the operating room. On reexploration it was seen that pronounced enlargement of the flank hematoma had occurred. Left nephrectomy was carried out and this controlled the retroperitoneal blood loss.

DR. MATHEWSON: *Dr. Steele, would you have carried out exploration of the left flank hematoma at the original operation?*

DR. STEELE: No, not necessarily. Our policy is to explore central hematomas and hematomas about the duodenum and pancreas where there may be a major visceral or vascular injury. We do not explore pelvic or flank hematomas as a matter of policy unless the hematomas appear to be arterial and are rapidly expanding. If pelvic hematomas are decompressed, massive uncontrollable venous hemorrhage may develop because the veins of the pelvis are injured more often than the arteries and are much more difficult to control. Once we open the flank hematoma, we may also end up with uncontrollable parenchymal blood loss from the kidney or renal venous injury which often requires nephrectomy for control. We recently reviewed the series at San Francisco General Hospital and believe that more kidneys are salvaged by conservatism than by entering the hematoma, since the late morbidity from failure to explore flank hematomas has been negligible. Provided we are ready to reintervene, no harm is done and more renal tissue will be salvaged.

DR. MATHEWSON: *Dr. Chapman, we have left the management of orthopedic injuries to the last. As an orthopedist, do you agree with this and what are your priorities for treating this compound fracture?*

MICHAEL CHAPMAN, MD:* I am afraid I must acknowledge our lack of priority. The other injuries are apt to be responsible for mortality so that plastic, maxillofacial, hand and orthopedic injuries assume the least priority. We would like to be called and to play a role in the initial assessment so that we can contribute to the development of priorities. Injuries such as a dislocated hip constitute a relative emergency but these often can be reduced in a minute or two after the induction of anesthesia in the operating room, which will not delay any general surgical procedure. We can also assist in the reduction or immobilization of fractures in the emergency room or shortly after the induction of anesthesia. This may improve circulation and prevent vascular complications which otherwise might result in the loss of an extremity. The importance of adequately immobilizing the femur fracture to prevent undue mortality has been well documented and, of course, this should be part of initial management of patients with such injuries.

We do not disagree with decisions to defer x-ray studies until the return to the radiology department the second time, but if possible we would prefer to see x-ray films of fractures done as part of the initial evaluation. As to the definitive management of the tibia and fibula in the case presented, the wound should be excised, debrided and irrigated preferably within six or eight hours of injury. We believe it is important to leave a wound associated with compound fractures open. This greatly simplifies the procedure and, we believe, avoids much of the hazard of infection. In this case, following debridement two "K" wires were placed—one in the proximal tibia and another in the calcaneus—and the fracture was immobilized in plaster.

We have been aggressive regarding immobilization of major fractures such as those of the femur so that a patient can be moved about and gotten out of bed. This also prevents many of the respiratory and cardiovascular complications that develop in multiply-injured patients in whom fractures are treated in traction.

I might add, finally, that six months after recovery from the general surgical injuries, the patient is often left with his orthopedic disability and this is what he remembers years later. If there is residual pain and paralysis, the patient may not remember that you saved his life but he may blame you for his disability. For this reason, it is important that the orthopedic surgeons and neurosurgeons be involved in the initial assessment of the patient.

DR. MATHEWSON: In summary, I would like to reemphasize the principle that, in a patient with multiple injuries, the senior surgeon with the most comprehensive knowledge of trauma should assume responsibility for the patient. He should carry out a rapid complete evaluation of the patient, then develop priorities for management of these. The priority is airway protection, second is cardiovascular resuscitation, then comes central nervous system examination and, finally, management of orthopedic and plastic injuries. Each of the specialists who are involved in a patient's care should have a chance to evaluate the patient initially and advise about management. By so doing, optimal care will be provided and minimal morbidity and mortality will result.

*Assistant Chief of Orthopedics and Assistant Professor of Orthopedic Surgery, University of California, San Francisco.

Refer to: Katz RL: Informed consent—Is it bad medicine? (Special Communication). West J Med 126:426-428, May 1977

Special Communication

Informed Consent
Is It Bad Medicine?

RONALD L. KATZ, MD
Los Angeles

As an anesthesiologist involved with informed consent every day, there are a number of problems I encounter. As a teacher, I hear students at varying levels raise questions relating to informed consent. As a result of my theoretical and practical involvement with informed consent I have been asked by The Western Journal of Medicine to share my views on the subject. While my perspective may sometimes focus on patients undergoing anesthesia and operation, it seems that some of my observations are relevant for patients and physicians in general.

In evaluating informed consent, one should look at the proposed benefits. One benefit to patients is said to be a better understanding of their disease and the procedures to be carried out. For physicians, a benefit is said to be protection in malpractice suits. The latter can be disposed of immediately. Having a signed informed consent form does not protect a physician. Time after time such forms have been repudiated on the witness stand by patients who claimed they did not remember signing the form or that they did not understand the form or that the form was signed under duress because they were ill. Having disposed of informed consent as a protection for physicians, let us now turn our attention to informed consent as protection for patients.

Many of us who deal with patients and routinely obtain informed consent are aware that much of the information we give a patient before an operation is either forgotten or remembered incorrectly. A few studies have begun to document this clinical impression that patients do not really understand or remember informed consent discussions. A recent study which has received much attention is that by Dr. George Robinson and Dr. Avraham Merav at Montefiore Hospital and Medical Center, New York City.[1,2] They found that no matter how carefully the possibilities of death, injury or complications were discussed, most patients did not accurately recall what they had been told.

Robinson and Merav referred to primary and secondary recall. Primary recall was based on the response of the patient to general questions concerning the informed consent conversation held preoperatively. Secondary recall involved the patients being given itemized lists of subjects concerning the preoperative interview and being asked to comment on whether or not this had been discussed and if so to state the substance of the conversation. The average recall for all categories discussed was 29 percent for primary recall and 42 percent for secondary recall. The worst scores were obtained in the category of potential complications. Here primary recall was only 10 percent, with secondary recall being 23 percent. Primary recall for the discussion of the diagnosis and the nature of the illness was 33 percent, with secondary recall being 46 percent. A discussion of the proposed operation had a primary recall of 26 percent and a secondary recall of 51 percent. Benefits of the proposed operation had a primary recall of 29 percent and a secondary recall of 47 percent. In addition to this failure to remember the informed consent interview, patients also were found to deny parts of the conversation, to make errors of attribution and to fabricate. The most common error after failure of recall or denial was fabrication. Patients quoted things that were never said or quoted promises never made. In some cases the patients were quite adamant that something which had never been said was in fact promised.

Having shown that patients do not remember very well the informed consent obtained from a preoperative interview, let us now consider whether informed consent may actually harm the patient. This is an area that is difficult to study. It is not possible to determine whether a postoperative complication was due to the anesthesia and operation or whether it was unrelated. There is, however, some suggestive evidence that some complications can be generated by the informed consent discussion and not by the anesthesia and operation. One example is a patient who during

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the course of an informed consent discussion was told that nausea and vomiting might occur postoperatively, in part because of the anesthetic and in part because of the nature of the operation. The next day induction with diazepam, which produced sleep, was carried out, but shortly after the patient was asleep the operation was cancelled. The only drug which the patient received was the diazepam. Immediately upon awakening, the patient complained of extreme nausea and began to retch. There was virtually continuous retching for 20 minutes. I was called to see the patient and explained that the proposed anesthesia and operation had not taken place and that the only drug she had received was diazepam, which does not normally produce nausea and vomiting, and in fact has an antiemetic action. As soon as the patient was informed that anesthesia and operation she had expected had not occurred, the nausea and retching immediately disappeared. The most likely explanation is that the informed consent discussion and the focusing on the nausea and vomiting was a form of posthypnotic suggestion occurring during the informed consent discussion.

A similar example is a patient who was to undergo a diagnostic procedure in which ketamine is used. During the preoperative discussion, the possible occurrence of the vivid bad dreams that ketamine sometimes produces was discussed. The patient asked many questions about the bad dreams and focused on this aspect of the discussion. Subsequently, the choice of anesthetic was changed because of a change in the proposed operative procedure and the patient was given an inhalation anesthetic. Postoperatively there developed what appeared to be a classic case of ketamine-induced hallucinations and bad dreams. Once again, pointing out to the patient that ketamine had not been used and that therefore we were surprised that he was having hallucinations and bad dreams resulted in a rapid recovery. While it is possible, although rare, to have such a response from forms of anesthesia other than ketamine, the most reasonable explanation here is that again the informed consent discussion concerning ketamine was responsible for the postoperative course of the patient.

Perhaps the most dramatic and clear-cut evidence of a postoperative complication induced by the informed consent discussion involves five patients seen over several years. In each case a spinal anesthetic had been chosen. The surgeon, in addition to the anesthesiologist, discussed the possibility of spinal headache and did so at great length and in extremely graphic terms. In each of these patients the decision to administer a spinal anesthesia was changed and a general anesthetic was substituted. Despite this, the five patients complained of severe postoperative headaches and described them in terms similar to those discussed by the surgeon preoperatively. In one of these cases, the "spinal headache" persisted for so long and was so intense that a neurosurgical consultation was obtained. The neurosurgical consultant who read the preoperative note in which it was stated that spinal anesthesia was to be used but failed to read the anesthetic record, wrote a two-page note describing the case as one of the most typical cases of spinal headache he had ever seen. It is also of interest that the operating surgeon who provided the vivid discussion of spinal headache stated that 100 percent of his patients who received spinal anesthesia had spinal headaches. In light of these five cases described above, this is not surprising.

Having shown that informed consent does not help physicians in malpractice cases, that preoperative informed consent discussions are not well remembered by patients and that complications may actually be generated by informed consent discussions, the logical question is should we continue to push forward the doctrine of informed consent? There are ever increasing suggestions to expand the boundaries of informed consent. At some hospitals (including my own) it is the practice to obtain an informed consent for surgical procedures and another one for anesthesia. It would be difficult to conceive of a patient who would be willing to undergo a major surgical operation (which could not be carried out under local anesthesia) but who would then balk at signing a consent for anesthesia. I have now seen patients, who inadvertently signed one consent but not the other, being subjected to a delay in operation because of the lack of both an anesthesia and a surgical signed consent form. In one case the patient begged to have his operation and wished to sign the second consent, but because he had already received preanesthetic medication it was felt that the second consent could not properly be signed.

A number of patients have complained to me that before a previous operation they had been told too much about the anesthesia and surgical procedure. They stated that they had come to

our institution because they had confidence in the institution and physicians and that they did not wish to hear a discussion of all of the complications. I think it is logical to ask the question "Why are we willing to harm so many patients for the few litigation-minded patients?" Should we not be tailoring our handling of the discussion with the patient for the vast majority of patients who do not intend to sue, rather than for those few who might? I would propose that we provide patients with reasonable explanations of what we feel is appropriate and not permit lawyers or administrators to set the rules. I further propose that we not force patients to sign meaningless pieces of paper to satisfy legal and bureaucratic requirements. I believe that the honesty and integrity of physicians and a good patient-physician relationship provide the best guarantees that patients will receive appropriate treatment. It seems to me that interposing legal-sounding documents between patient and physician can only serve to harm the patient-physician relationship and the patient.

REFERENCES

1. Patient consent given—but forgotten—MDs urged to document pre-op discussions. Med World News, Feb 23, 1976, p 26

2. Robinson G, Merav A: Informed consent—Recall by patients tested postoperatively. Ann Thorac Surg 22:209-212, Sep 1976

First Aid for Esophageal Burns

Dr. Ritter: I'd like to ask what you might tell a mother who calls you and tells you that her youngster has probably taken the top off a can of a solid corrosive. He's crying. The can is open. The mother is certain that the youngster has gotten some of it into the mouth because he's spitting, and there's maybe a little blood in the oral cavity itself. . . . Dr. Cohen: . . . You must know what substance the child has taken. . . . If the parents tell you, for instance, it is a catalyst, or if they tell you it is lye, or that it is a strong detergent, then it will immediately tell you whether it is a base or an acid, and what you should tell the parents about the antidote. The one thing you do tell them is: "Do *not* make your child vomit." That's the tendency for the antidotes on labels. But vomiting moves this noxious agent up and down the esophagus and produces more difficulty. All people have orange juice, or vinegar, or milk products around the house. Those are the things you tell them to give the child immediately, or copious quantities of water, and get them to an emergency room.

—FRANK N. RITTER, MD, *Ann Arbor*
SEYMOUR R. COHEN, MD, *Los Angeles*
Extracted from *Audio-Digest Otorhinolaryngology*, Vol. 10, No. 1, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1577 East Chevy Chase Drive, Glendale, CA 91206.

BOOK REVIEWS

THE WESTERN JOURNAL OF MEDICINE does not review all books sent to it by the publishers. A list of new books received is carried in the Advertising Section.

REVIEW OF ALLIED HEALTH EDUCATION: I—General Editor: Joseph Hamburg, MD, Dean, College of Allied Health Professions, University of Kentucky; Associate Editors: Darrel J. Mase, PhD, Professor, Division of Health Systems Research, University of Florida College of Health Related Professions; and J. Warren Perry, PhD, Dean, School of Health Related Professions, State University of New York at Buffalo, and Editor, **Journal of Allied Health.** The University Press of Kentucky, Lexington (40506), 1974 234 pages, $7.50.

This book is one in a planned series designed to provide a common literature on allied health education. The editors describe this review as the first of a series to "provide a current appraisal of the developments in allied health education and research," which it is hoped will "seek to help bind the health professions into a true alliance." In general, this volume does accomplish the first of its purposes through an historical and philosophical review of five major allied health professions (dental, radiologic technology, clinical laboratory technology, physician's assistant and occupational therapy). The three objectives stated for this volume are noble and inspiring. However, it is likely that only portions of the information may help to create "new levels of understanding for students, educators and practitioners." In light of the listed objectives, one may be inclined, upon completion of this book, to rank allied health education somewhere between delight and doom.

Dr. Pelligrino (as well as Drs. Jacques and Perry) summarize, in an exemplary and delightful manner, the concepts and concerns central to the utilization of manpower in curing and preventing illness of the health care population. Much that is said by these authors within the first two chapters is not new; rather, it might be said that their thoughts are contrary to many beliefs and views, and thus could be considered as innovative. The willingness of the professions to dissolve boundaries and collapse overlapping tasks and responsibilities has not occurred with earthshaking speeds—for a variety of rational and irrational reasons. In a subsequent chapter, Dr. Samuel Martin raises the essential questions of economics of health care relative to various professionals. The costs of providing care would seem to obviate against the escalation of inordinate numbers of professional careers, and the author's call for more experience with pricing and entrepreneurships provides stimulating thoughts for the truly cost-conscious professional.

A feeling of doom settles in, however, as one begins to complete the remaining chapters on the individual allied health professions. The complexities which have evolved within as well as between professional disciplines smacks of the realities to be overcome if indeed "allied" health will ever live up to its appellation. The text demonstrates that allied health has been fraught by miscommunication and fragmentation, and is further aggravated by developing specialties within professional ranks.

For a more logical and efficient utilization of manpower in providing care, the issues raised by the authors above command resolution before any future development and expansion of the professions. Perhaps one neglected factor requiring attention is the realm of power. Professionals may do well to look beyond their selfish boundaries and attempt to answer, Who has the power over life? As one of the authors states, the time has come to "get it all together" . . . "our survival depends upon it." These issues are of crucial importance—not only to the future developments of "allied" health education, but also to the changing scene of medical practice.

This volume may be helpful to those new to the field of allied health. It is undoubtedly incomplete, and no attempt was made to cover the myriad facets of allied health. Future reviews may prove to be valuable in providing for a common literature where the broad issues relating to this vast complex can be appropriately addressed.

ALMA S. EVANS
Assistant Director of Evaluation
Area Health Education Center
University of California, San Francisco

* * *

HUMAN ENDOCRINOLOGY—A Developmental Approach—Dorothy B. Villee, MD, Department of Pediatrics, Harvard Medical School. W. B. Saunders Company, West Washington Square, Philadelphia (19105), 1975. 479 pages, $16.75.

The theme of this text is the influence of maturation and the changes in cell machinery on the mechanisms by which endocrine and metabolic abnormalities are mediated. It provides a needed emphasis on the importance of age as a determinant in the clinical expression of endocrine and metabolic disorders.

The book is divided into five major parts. In Part One, "The Fetus," fertilization, embroyogenesis, the placenta, organogenesis of the endocrine glands and endocrine control of fetal metabolism and differentiation are discussed. Part Two, "The Newborn," concerns the endocrine and metabolic changes of the perinatal period, disorders of carbohydrate metabolism in the newborn, the adrenal gland of the newborn, and abnormalities of sexual differentiation. The homeostasis of water and electrolytes, the homeostasis of glucose, and the biochemical basis of growth and its control are considered in Part Three, "The Child." Part Four, "The Adolescent," deals with bone metabolism, calcium homeostasis, the influence of sex hormones on skeletal maturation, sexual maturation and reproduction. In Part Five, "Postmaturation and Senescence," adult onset diabetes, osteoporosis, male climacteric, menopause, obesity, atherosclerosis, hypertension, structural changes with age and neoplastic disorders are discussed. Discussion of physiologic hormonal regulation is followed by examples of clinical disorders.

A criticism of the book relates to the reference style used. Each chapter is followed by a list of standard references with commentary on the value of each. After some chapters, a list of pertinent selections from the literature is included. Although this style is consistent with the stated intention of the author, the inclusion of references specific for the data given in the text would have enhanced the book's value as a reference source.

The information is presented in a concise, informative and readable manner. The book affords a real opportunity to gain knowledge for a variety of readers in addition to the medical students for which it was intended, that is, interns and residents, pediatricians and family physicians. Doctor Villee has been successful in her goal to present an overview of the regulatory influence of hormones as life unfolds in logical sequence from procreation to death.

ROBERT PENNY, MD
Department of Pediatrics
University of Southern California
School of Medicine
Los Angeles

in memoriam

Baker, Sol Ronald, Beverly Hills. Died March 14, 1977, aged 66. Graduate of the University of Michigan Medical School, Ann Arbor, 1935. Licensed in California in 1936. Dr. Baker was a member of the Los Angeles County Medical Association.

Chamberlain, Herbert E., Sacramento. Died January 1, 1977 in Sacramento, aged 83. Graduate of Harvard Medical School, Boston, 1921. Licensed in California in 1937. Dr. Chamberlain was a member of the Sacramento County Medical Association.

Fallon, John A., Los Angeles. Died November 19, 1976 in Los Angeles of cancer, aged 70. Graduate of the University of Toronto Faculty of Medicine, 1929. Licensed in California in 1947. Dr. Fallon was a member of the Los Angeles County Medical Association.

Gallup, Palmer R., San Bernardino. Died September 16, 1976 of heart disease, aged 66. Graduate of the University of Nebraska College of Medicine, Omaha, 1935. Licensed in California in 1939. Dr. Gallup was a provisional member of the San Bernardino County Medical Society.

Irwin, Willis Robert, Poway. Died February 25, 1977 in Poway in an automobile mishap, aged 58. Graduate of the Creighton University School of Medicine, Omaha, 1952. Licensed in California in 1953. Dr. Irwin was a member of the San Diego County Medical Society.

Kirlin, Laurence P., Santa Clara. Died March 11, 1977 in San Jose of diabetes, aged 70. Graduate of the Creighton University School of Medicine, Omaha, 1933. Licensed in California in 1940. Dr. Kirlin was a member of the Santa Clara County Medical Society.

LeMoncheck, Edward, Los Angeles. Died December 10, 1976 in Los Angeles of heart disease, aged 61. Graduate of New York University College of Medicine, New York, 1941. Licensed in California in 1942. Dr. LeMoncheck was a member of the Los Angeles County Medical Association.

Molloy, Joseph E., Santa Clara. Died September 22, 1976 of myocardial infarction, aged 55. Graduate of Rush Medical College, Chicago, 1945. Licensed in California in 1968. Dr. Molloy was a member of the Santa Clara County Medical Society.

Morse, Harold Abner, Oakland. Died February 4, 1977, aged 82. Graduate of the University of California Medical School, Berkeley-San Francisco, 1924. Licensed in California in 1924. Dr. Morse was a retired member of the Alameda-Contra Costa Medical Association.

Murphy, Edward Lee, Burbank. Died December 18, 1976 in Burbank of heart disease, aged 76. Graduate of Rush Medical College, Chicago, 1935. Licensed in California in 1946. Dr. Murphy was a member of the Los Angeles County Medical Association.

Ostroff, Robert Allison, Los Angeles. Died March 18, 1977, aged 83. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1919. Licensed in California in 1919. Dr. Ostroff was a member of the Los Angeles County Medical Association.

Parks, Kirtland Garvin, Long Beach. Died February 9, 1977 in Long Beach of carcinoma of sigmoid of the colon, aged 80. Graduate of the University of Oklahoma School of Medicine, Oklahoma City, 1923. Licensed in California in 1925. Dr. Parks was a member of the Los Angeles County Medical Association.

Paterson, Adam, San Leandro. Died March 2, 1977 in San Leandro of pneumonia-metastatic disease, aged 77. Graduate of the University of Glasgow Medical Faculty, 1930. Licensed in California in 1931. Dr. Paterson was a member of the Alameda-Contra Costa Medical Association.

Rosenberg, Harold Samuel, San Francisco. Died March 5, 1977 in San Francisco of leukemia, aged 38. Graduate of New York Medical College, New York, 1963. Licensed in California in 1964. Dr. Rosenberg was a member of the San Francisco Medical Society.

Sedgwick, Virgil DeMott, Long Beach. Died February 5, 1977 in Long Beach of cerebrovascular accident, aged 76. Graduate of the University of California Medical School, Berkeley-San Francisco, 1926. Licensed in California in 1926. Dr. Sedgwick was a retired member of the Los Angeles County Medical Association.

Shankman, Irwin M., Vallejo. Died March 2, 1977 in Green Valley, aged 68. Graduate of the University of Manitoba Faculty of Medicine, Winnipeg, 1934. Licensed in California in 1948. Dr. Shankman was a member of the Solano County Medical Society.

Sullivan, Norman Ross, Santa Cruz. Died March 11, 1977 in Santa Cruz, aged 88. Graduate of the University of Illinois College of Medicine, Chicago, 1911. Licensed in California in 1923. Dr. Sullivan was a retired member of the Santa Cruz County Medical Society.

Thorpe, Franklyn, Los Angeles. Died February 12, 1977 in Los Angeles of cerebrovascular accident, aged 84. Graduate of Tufts College Medical School, Boston, 1922. Licensed in California in 1929. Dr. Thorpe was a member of the Los Angeles County Medical Association.

Van Orden, Max T., Los Angeles. Died March 13, 1977, aged 61. Graduate of Northwestern University Medical School, Chicago, 1941. Licensed in California in 1946. Dr. Van Orden was a member of the Los Angeles County Medical Association.

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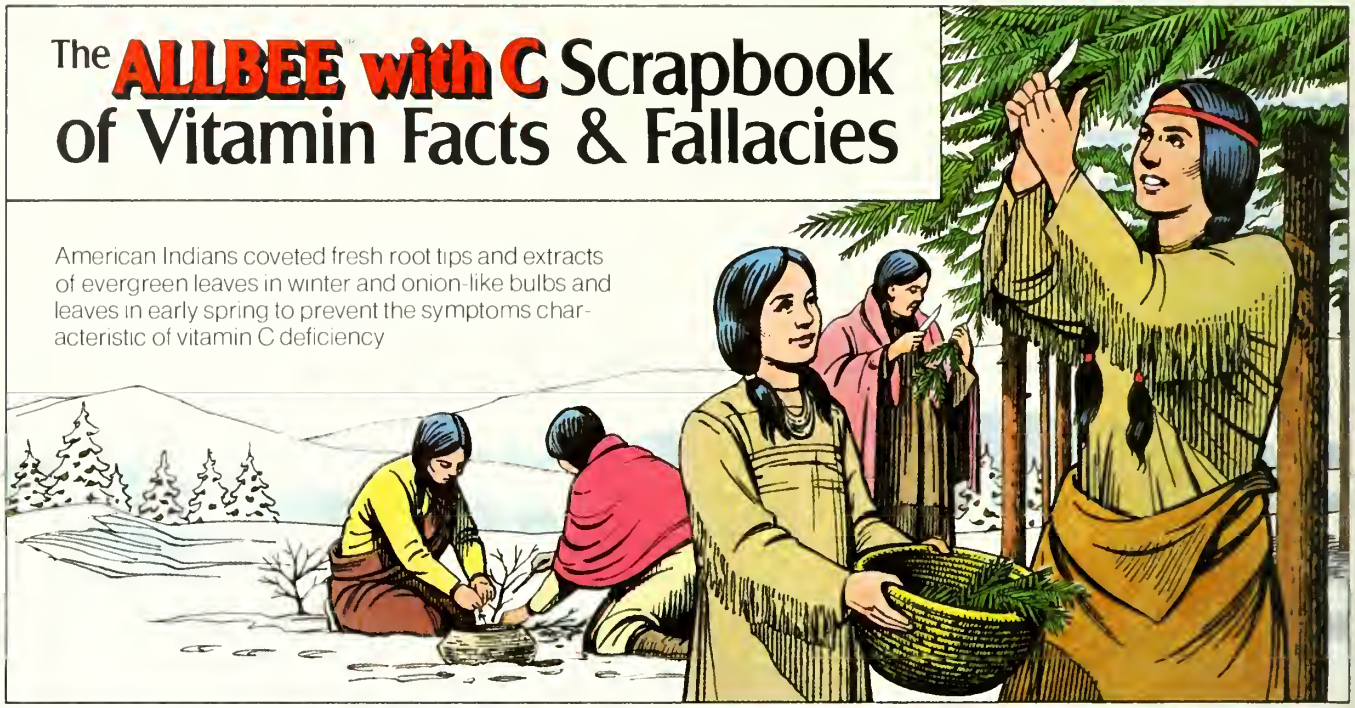
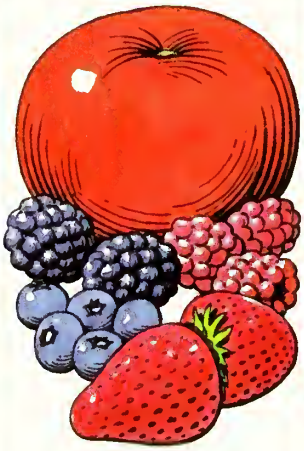
The ALLBEE with C Scrapbook of Vitamin Facts & Fallacies

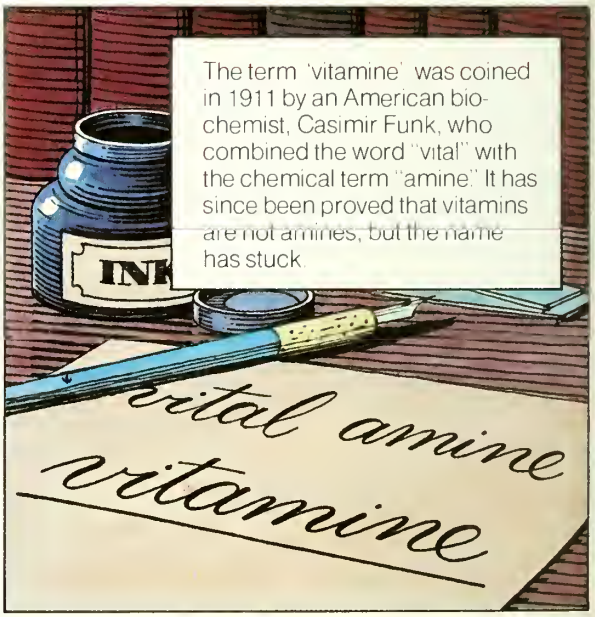
American Indians coveted fresh root tips and extracts of evergreen leaves in winter and onion-like bulbs and leaves in early spring to prevent the symptoms characteristic of vitamin C deficiency



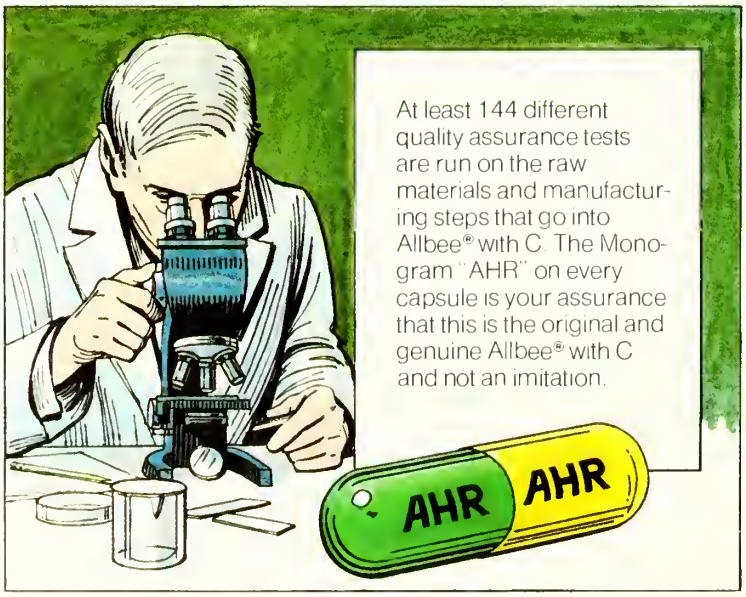


A tomato is botanically classified as a berry!

It is ironic that many of the vegetables highest in vitamin C and riboflavin are considered unappetizing by many people. These include turnip greens, kale, chard, mustard greens, spinach, water cress, broccoli and brussels sprouts.



The term 'vitamine' was coined in 1911 by an American biochemist, Casimir Funk, who combined the word "vital" with the chemical term "amine." It has since been proved that vitamins are not amines, but the name has stuck.



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CARDIOLOGIST to share office including fully equipped non-invasive laboratory, and hospital practice located in a medical and cultural center adjoining Los Angeles. Must be CV Board certified or eligible and expert cath person. Salary or percentage first year. Partnership available after 1 year. Please send C.V. Box No. 9516, Western Journal of Medicine, 731 Market St., S.F., CA 94103.

FACULTY POSITION open for Family Physician in Family Practice Residency Program. Bd. eligible or Bd. certified. Salary range $40,000 to $50,000, plus excellent fringe. 4 weeks vacation plus min. of 2 weeks postgraduate education time per year. Practice ½ time and teach ½ time. Contact William Walsh, MD, Director, UCLA-Antelope Valley Hospital Medical Center Family Practice Residency Program, 44241 N. 15th St. West, Lancaster, Calif., (805) 948-5971.

WANTED: FAMILY PRACTITIONER AND OB-GYN SPECIALIST in McMinnville, Oregon in the Willamette Valley 35 miles from Portland. In the middle of hunting and fishing area. 13,000 population, 40,000 drawing area. Modern open staff hospital. Dr. James D. Treneman, 1300 N. Adams St., McMinnville Ore. 97128. Phone (503) 472-4647, eves. (503) 472-7676.

PHYSICIAN CLINICAL PREVENTIVE MEDICINE, nutrition and metabolic diseases. Excellent immediate and future opportunity in joining huge, clinical, Inc., practice in southern California. Send Curriculum Vitae to W. D. Currier, MD, Inc., 301 E. Colorado Blvd., Pasadena, CA. 91101. (213) 578-0531.

NORTHERN CALIFORNIA PRACTICE OPPORTUNITIES FOR PRIMARY CARE PHYSICIANS AND SELECTED SPECIALISTS—Redding, California, offers excellent practice opportunities for physicians who want a good community for their families, a close knit medical community, a variety of outdoor sports and a chance to build a strong practice. Hospitals (3) are modern, full service, high quality institutions and there is a well developed emergency system. The rapid growth of the area has produced a need for physicians in these categories: General Practice, Internal Medicine, Medical Oncology, Pediatrics, Orthopedics, Neurosurgery, OB-Gyn and Neurology. For further information, contact the Physician Recruitment Committee, Mercy Medical Center, Clairmont Heights, Redding, California 96001.

CALIFORNIA—NEUROSURGEON. University-affiliated program seeking Head of Neurosurgery. Geographic full-time. Good compensation. Professional liability insurance paid. Thriving medical center. Delightful city near national parks. Equal Opportunity Employer. Send curriculum vitae in first letter to Jerome S. Harris, MD, Director of Medical Affairs, Assistant Dean, Valley Medical Center, 445 S. Cedar Ave., Fresno, CA 93702.

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PHYSICIAN, AMBULATORY CARE: Vacancy exists in Ambulatory Care Service of a 200-bed GM&S hospital in Livermore area. Salary dependent on experience and qualifications. Attractive benefits include retirement system, health and life insurance, liberal leave system, provision for paid continuing education. Contact Personnel Department, Veterans Administration Hospital, Livermore, CA 94550. Phone 415-447-2560, X 304/305.

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(Continued on Page 30)

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(Continued from Page 29)

PHYSICIANS WANTED

PRIMARY CARE PHYSICIANS and some specialists needed immediately in Texas. Generous guarantees, assistance with office overhead, relocation, etc. Send C.V. and photo to The Rural Doctors Group, Inc., 507 First Federal Plaza, Dept. W, Austin, Texas 78701.

FAMILY PRACTITIONERS wanted for fresh approach to Primary Care. All administrative headaches eliminated. No financial risks. Hospital-based practices in several Northern California areas with variety of town sizes and climates. FFS with $40,000 annual guarantee, life, health and disability insurance; pension plan; moving expenses. Minimal nightcall; ER back-up. Contact EMS, 3661 Sacramento St., Dept. D, San Francisco, CA 94118. (415) 921-9000.

SURGEON with Family or General Practice interest to join a growing rural group practice in Northwest Montana; modern clinic and 30 bed hospital; mountainous setting and ideal climate; foundation sponsorship, no investment required; fringe benefits. Write P. A. Hinton, Administrator, or J. Michael Wise, MD, Medical Director, Mission Valley Health Services, St. Ignatius, MT 59865.

MICRONESIA—Immediate opportunities exist in the Trust Territory of the Pacific Islands for Internists, Surgeons, Pediatricians and General Practitioners. These are two-year assignments with housing and family travel provided. For applications, contact: Trust Territory Office, Bldg. 112, Fort Mason, San Francisco, CA 94123.

GENERAL SURGEON, Board Certified or eligible. Opportunity to develop independent surgical practice and share call with established surgeons in area. Sierra Nevada foothill community 40 minutes from Sacramento. Box 5924, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

FAMILY PRACTICE PHYSICIANS for rural group practices in Placerville, California, and other California sites. Practices will be staffed by health care teams utilizing nurse practitioners and physician assistants, and physician contracts will be with the FCHS, a public, nonprofit foundation. Income $35,000 per year plus incentive fees to $40,000 based on productivity and quality of care; generous fringe benefits; paid full malpractice; and all administrative services provided. Contact: Len Hughes Andrus, MD or Bill D. Burr, MD, Foundation For Comprehensive Health Services, 1570 Response Road, Suite 2082, Sacramento, CA 95815.

FAMILY PRACTITIONER needed to replace retiring member of Six man Medical Corporation. Small metropolitan area. Very friendly with close proximity to big Cities and beaches. Local City College and 4 year College with all social amenities and sport. 4½ day week, prepaid malpractice, on call shared by all in group. Competitive salary 1st year—full corporate stock holdership after 1st year. Full Corporate benefits immediately. Write: B. R. Ericsson, MD, Manor Medical Group, Inc., 223 China Grade Loop, Bakersfield, CA 93308.

OB/GYN for Medical Group. Complete x-ray and laboratory facilities. Starting salary $4,000 per month with increments to follow until eventual partnership is reached. Free health and accident insurance, and medical association dues. Contact Mr. Fine, 2675 E Slauson Ave., Huntington Park, CA 90255. (213) 589-6681.

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CLINICAL ALLERGIST, not immunologist, leaving large, 30-year practice. Wants part-time allergy oriented work. Will do allergy work-ups, antigen dilutions and directions, follow-ups, etc. Interested in Northern California only, smaller towns preferred. Write Box No. 5921, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

INTERNIST, ABIM. Background cardiovascular disease, executive health examination, risk factor eval./preventive regimens, insurance medicine. Desires San Francisco or mid Peninsula, salaried part-time position. Mondays, Wednesdays, Fridays preferred. Available 13 June. Write Box No. 9520, Western Journal of Medicine, 731 Market St., S.F., CA 94103.

INTERNIST available for work in Bay Area. EKG reading and some teaching desirable. Reply to Box No. 9519, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

FAMILY PRACTITIONER, 51, Board certified, seeks opening in or near Bay Area, San Diego, or Los Angeles. Box No. 5925, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

ANESTHESIOLOGIST. Board certified, 36. Experienced in open heart and ICU on staff northeastern teaching hospital wishes to relocate to private group in metropolitan area with good weather. Please reply to Box No. 5923, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

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YOUNG FAMILY PRACTITIONER seeks another to share busy, varied practice, 3-day week and mellow night call with time to enjoy beautiful South Whidbey Island. Rural living, but only 45 miles to Seattle. Good hospital and support services. Steve Shapiro, MD, The Langley Clinic, P.O. Box 137, Langley, WA 98260, (206) 321-5272.

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LOCUM TENENS wanted 1st two weeks June '77 prefer Bay Area or Sierra. ABFP certified. P.O. Box 64, New York Mills, Minn. 56567.

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A MEDICAL OFFICE in a modern medical complex near John Muir Memorial Hospital in Walnut Creek, Calif. is available for lease or sale at reasonable price as of approximately September 1977. Call (415) 939-9400.

MEDICAL SUITES AVAILABLE—Foothill Medical Buliding, 21297 Foothill Blvd., Hayward, Calif. One 850 sq. ft. and one 760 sq. ft. Each has a doctors office, nurse's station, waiting room, and three treatment rooms. The building has an X-Ray, medical laboratory, and a pharmacy. It is ideal for a general practitioner or an internist. Some free rent. For information call (415) 582-6942.

MEDICAL AND LABORATORY SPACE available in well maintained Medical Dental building in Whittier, CA. Area in demand of additional practitioners. (213) 698-2285.

SHERMAN OAKS, CALIFORNIA. 4955 Van Nuys Blvd. Medical building near freeway, next door to Hospital. Building has pharmacy, bank, doctors, optician. Superb suites—has to be seen to be appreciated. Buckeye Realty & Management Corp. Mr. Richards. (213) 652-1411.

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MEDICAL SUITE—651 sq. feet, corner in complex with 4 Internists, 2 GP's, Orthopedist, Clinical Laboratory, Dentist, Physical Therapist, Maintenance, all utilities excepting electricity furnished. I. N. Tucker, MD, 25 Evergreen, Mill Valley, CA 94941. Tele: (415) 388-3088.

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THIS LISTING of continuing education programs in California and Hawaii is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Committee on Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103; or phone (415) 777-2000, ext. 146. For a list of organizations approved for Category I credit toward the CMA Certificate in Continuing Medical Education or for more information on accreditation or certification, please write to the above address.

CANCER

May 21-22—**Management of Cancer—3rd Annual Workshop.** Institute for Cancer and Blood Research and Century City Hospital Radiation Therapy Center at Riviera Country Club, Pacific Palisades. Saturday-Sunday. 16 hrs. Contact: Howard R. Bierman, MD, Sci. Dir., Institute for Cancer and Blood Research, 140 N. Robertson Blvd., Beverly Hills 90211. (213) 655-4706.

June 3—**DES—Effects of Intrauterine Exposure to Synthetic Estrogens in Female Offspring.** Calif. Dept. of Health, Ad Hoc Advisory Committee on DES and Health Training Centers; Calif. Division, American Cancer Society, at Hyatt Regency Hotel, San Francisco. Friday. 7 hrs. $35. Contact: E. Fasal, MD, 2151 Berkeley Way, Rm. 704, Berkeley 94704. (415) 843-7900, ext. 656.

June 20-24—**Head and Neck Oncology.** UCLA. Monday-Friday.

August 10—**G. I. Carcinoma.** LLU. Wednesday. 4 hrs. $25.

September 17—**Clinical Implications of New Diagnostic Techniques—Ultrasound, Cat Scan, Radioisotopes, Clinical Chemistry.** San Francisco Regional Tumor Foundation at Fireman Fund Building, San Francisco. Saturday. 4 hrs. Contact: Norma Schlager, PhD, S.F. Regional Tumor Foundation, 14th and Lake, San Francisco 94118. (415) 221-2132.

October 3-7—**Medical Oncology Review.** American College of Physicians and Huntington Memorial Hospital at Huntington Sheraton Hotel, Pasadena. Monday-Friday. 36 hrs. $140, ACP members; $200, nonmembers. Contact: Arlene Ellis, Coord., Med. Staff Affairs, Huntington Mem. Hosp., 100 Congress St., Pasadena 91105. (213) 440-5176.

MEDICINE

May 15-18—**American Thoracic Society—Annual Scientific Meeting.** Hilton Hotel, San Francisco. Sunday-Wednesday. Contact: Mr. S. R. Iannotta, Assoc. Ex. Dir., ATS, 1740 Broadway, New York 10019. (212) 245-8000.

May 18—**Atherosclerosis and Diet: A Practical Pediatric Approach.** American Heart Assn., Greater Los Angeles Affiliate; L.A. Pediatric Society at Bonaventure Hotel, Los Angeles. Wednesday. 6 hrs. Contact: Nancy Brown, AHA, Greater L.A. Affiliate, 2405 W. 8th St., Los Angeles 90057. (213) 385-4231.

May 20—**American Heart Association, California Affiliate—Scientific Sessions for Physicians.** Hyatt House, San Jose. Friday. Contact: Marilyn Probst, Admin. Asst., AHA, Calif. Affiliate, 1370 Mission St., San Francisco. (415) 626-0123.

May 20—**Stomatology.** STAN. Friday. 6 hrs.

May 20-21—**Hematology.** UCSF. Friday-Saturday.

May 21—**EKG Workshop.** PMC at Miyako Hotel, San Francisco. Saturday.

May 21—**Pulmonary Artery Catheters and Ventilators.** PMC. Saturday.

May 27-29—**New Concepts in Clinical Electrocardiography.** American College of Cardiology at Century Plaza Hotel, Los Angeles. Friday-Sunday. Contact: Mary Anne McInerny, Dir., Dept. of Cont. Ed. Prog., ACC, 9650 Rockville Pike, Bethesda, MD 20014.

June 1-July 27—**Review of ACP Medical Knowledge Self Assessment Test IV.** PMC. Wednesdays, 7-10 p.m.

June 6-October 18—**Intensive Review of Recent Advances in Internal Medicine—3rd Annual.** UCLA. Monday evenings.

June 7-10—**Echocardiography—Fundamentals and New Developments in Cardiac Ultrasound.** American College of Cardiology at Town and Country Hotel, San Diego. Tuesday-Friday. Contact: Mary Anne McInerny, Dir., Dept. of Cont. Ed. Prog., ACC, 9650 Rockville Pike, Bethesda, MD 20014.

June 9-11—**Concepts and Controversies in Cardiology—1977.** Hospital of the Good Samaritan and American Heart Assn. of Greater L.A. at Hospital of the Good Samaritan, Los Angeles. Thursday-Saturday. Contact: Janie Sternal, Coord., CME, Hosp. of the Good Samaritan, 616 S. Witmer, Los Angeles 90017. (213) 488-8123.

KEY TO ABBREVIATIONS AND SYMBOLS

Medical Centers and CMA Contacts for Information

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103. (415) 777-2000.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Duane Dillman, PhD, Director, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 564-5911, ext. 391.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr., MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, Ext. 2400.

PMC: Pacific Medical Center
Contact: Martin Brotman, MD, Chairman, Education Committee, Pacific Medical Center, P.O. Box 7999, San Francisco 94120. (415) 563-4321, ext. 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Neil C. Andrews, MD, Chairman, Department of Postgraduate Medicine, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, California College of Medicine, Irvine
Contact: Robert Combs, MD, Associate Dean, Continuing Medical Education, University of California, Irvine—California College of Medicine, Irvine 92717 (714) 833-5991.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, P.O. Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: David Allan, MD, Associate Dean for Continuing Medical Education, 1309 Basic Sciences Building, University of California, San Diego, School of Medicine, La Jolla 92037. (714) 452-3708.

UCSF: University of California, San Francisco
Contact: Malcolm S. M. Watts, MD, Associate Dean and Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 226-2047.

June 18—**Allergy for the Office Practice.** PMC. Saturday.

June 24-26—**Dermatomycology.** UCSF. Friday-Sunday. 14 hrs. $250.

July 1-3—**Arthritis Education Workshop.** STAN. Friday-Sunday.

September 7-11—**Medical Knowledge Self-Assessment Program Course.** American College of Physicians at Golden Gateway Holiday Inn, San Francisco. Wednesday-Sunday. 30 hrs. $140, ACP members; $200, nonmembers. Contact: ACP, 4200 Pine St., Philadelphia, PA 19104.

September 14-16—**Pediatric Dermatology.** STAN. Wednesday-Friday. 23 hrs. $225.

September 26-30—**Medical Knowledge Self-Assessment Program Course.** American College of Physicians at Hilton Hotel, Los Angeles. Monday-Friday. 30 hrs. $140, ACP members; $200, nonmembers. Contact: ACP, 4200 Pine St., Philadelphia, PA 19104.

September 29-30—**Annual Physician Postgraduate Symposium on Heart Disease.** San Francisco Heart Assn. and Council on Atherosclerosis, American Heart Assn., at Golden Gateway Holiday Inn, San Francisco. Thursday-Friday. Contact: Molly Austin, Assoc. Dir., S.F. Heart Assn., 421 Powell, San Francisco 94102. (415) 433-2273.

September 29-30—**Clinical Immunology/Rheumatology Update.** UCSF. Thursday-Friday.

October 1-8—**Cardiology.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 29 hrs. $300.

October 3-7—**Medical Oncology Review.** See Cancer, October 3-7.

October 5-6—**American Heart Association, Greater Los Angeles Affiliate—45th Annual Fall Symposium and 10th Annual Griffith Lecture.** Hilton Hotel, Los Angeles. Wednesday-Thursday. 12 hrs. $65, member of any Heart Assn.; $85, nonmember. Contact: LaVerna Titus, AHA, Greater L.A. Affiliate, 2405 W. 8th St., Los Angeles 90057. (213) 385-4231.

October 6-7—**Pediatric Nephrology.** UCSF. Thursday-Friday.

October 8-9—**Practical Nephrology.** UCLA. Saturday-Sunday.

October 8-15—**Endocrinology/Nephrology Review.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 29 hrs. $300.

October 10-14—**Practical Electro-Cardiography.** Memorial Hospital Medical Center of Long Beach-UCI at Hotel Inter-Continental, Maui, Hawaii. Monday-Friday. $150. Contact: Exec. Sec., Center for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

October 21-22—**Diabetes.** STAN and Santa Clara County Diabetes Society. Friday-Saturday.

October 26—**Consultations in Hypertensions.** UCSD at Vacation Village, San Diego. Wednesday.

November 3-6—**California Society of Internal Medicine—Annual Meeting.** Canyon Hotel, Palm Springs. Thursday-Sunday. Contact: CSIM, 703 Market St., Suite 1412, San Francisco 94103. (415) 362-1548.

November 4-5—**Venous Thromboembolism.** PMC at Fairmont Hotel, San Francisco. Friday-Saturday.

November 7-11—**Pediatric Allergy and Clinical Immunology.** UCSF. Monday-Friday.

November 9—**Endocrinology Seminar.** LLU. Wednesday. 4 hrs. $25.

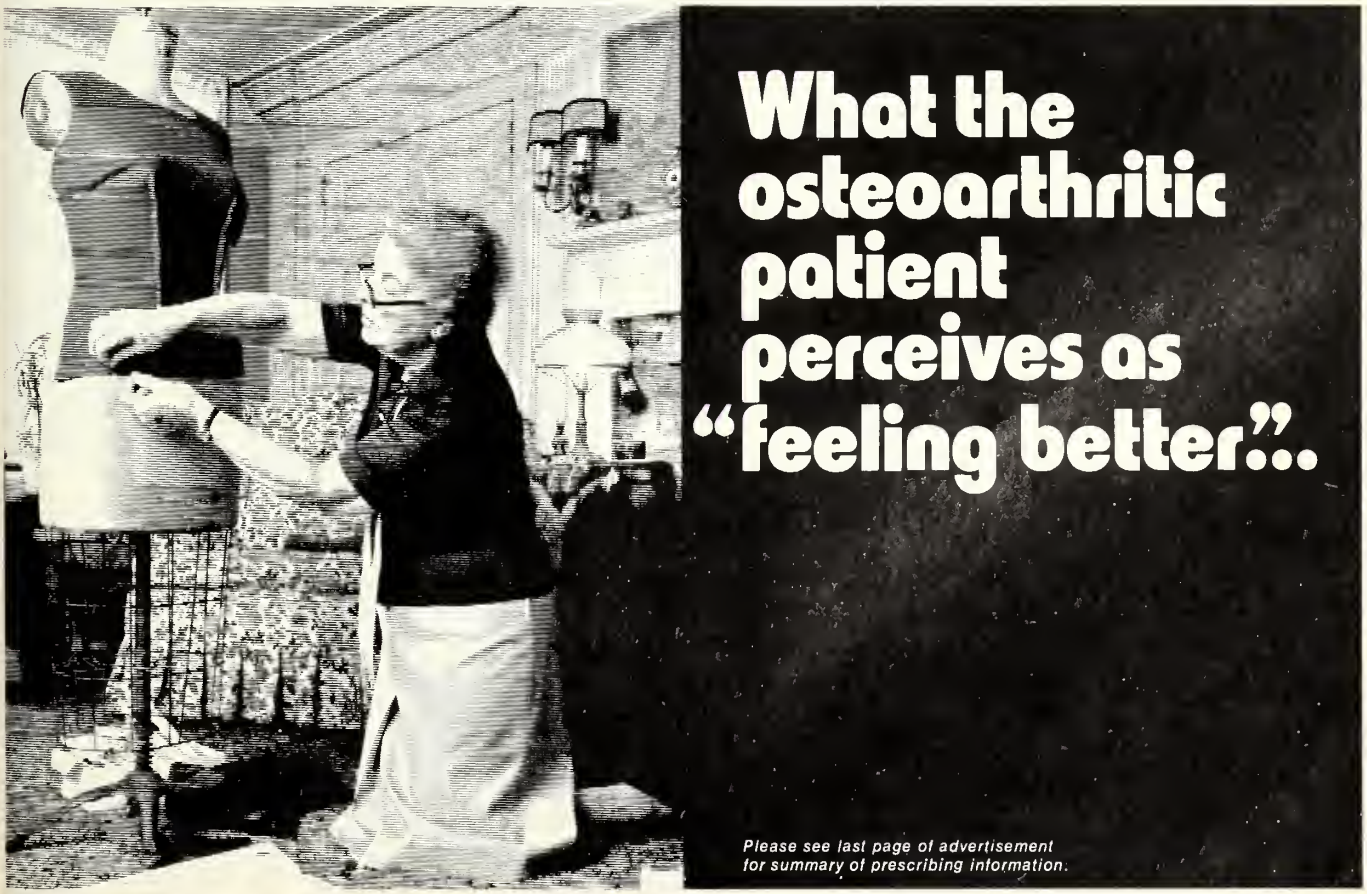
November 12-13—**Practical Rheumatology.** UCLA. Saturday-Sunday.

November 26-December 3—**Lymphoproliferative Disorders.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 29 hrs. $300.

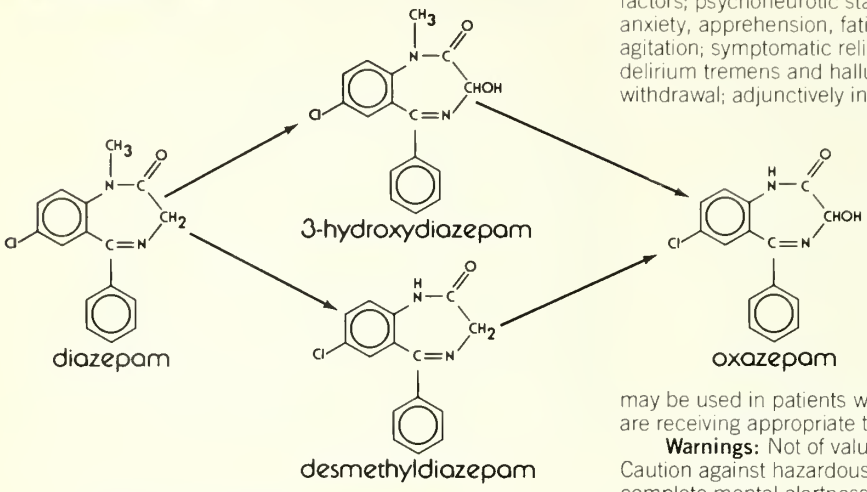
December 1-3—**Infectious Disease.** UCSD at Hilton Inn, San Diego. Thursday-Saturday.

December 7—**Lyman A. Brewer III Cardiothoracic Symposium**

(Continued on Page 35)



A pharmacokinetic character all its own



Valium (diazepam) is a benzodiazepine with a distinctive pharmacokinetic profile

The pharmacokinetic profile of Valium is one of the characteristics that sets it apart from other benzodiazepines. Consider, in particular, the metabolic pathway of Valium. The three major metabolites of Valium exhibit significant pharmacologic activity—and so, of course, does the parent substance—diazepam itself. All combine to produce the characteristic clinical response seen with Valium. The response you have come to know, to want and to trust.

Pharmacokinetic studies also demonstrate that Valium has a pattern of absorption, distribution, metabolism and elimination that is reliable and consistent. And, although the pharmacokinetics of a drug cannot, at present, be specifically related to its clinical effects, it is clearly a factor that distinguishes one product from another by providing important insights into how each moves through the patient's body.

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Before prescribing, please consult complete product information, a summary of which follows:

Indications: Tension and anxiety states; somatic complaints which are concomitants of emotional factors; psychoneurotic states manifested by tension, anxiety, apprehension, fatigue, depressive symptoms or agitation; symptomatic relief of acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in skeletal muscle spasm due to reflex spasm to local pathology; spasticity caused by upper motor neuron disorders; athetosis; stiff-man syndrome; convulsive disorders (not for sole therapy).

Contraindicated: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms (similar to those with barbiturates and alcohol) have occurred following abrupt discontinuance (convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence.

***Usage in Pregnancy:* Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Precautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed; drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.

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(Continued from Page 33)

—3rd Annual. LLU at Hilton Hotel, Los Angeles. Wednesday. 8 hrs. $50.

OBSTETRICS AND GYNECOLOGY

May 30-June 1—**New Concepts in Neonatal Monitoring.** USC at MGM Grand Hotel, Las Vegas. Monday-Wednesday. Contact: Mary V. Troyer, c/o Edward H. Hon, MD, Women's Hospital, 1240 N. Mission Rd., Los Angeles 90033.

June 3—**DES—Effects of Intrauterine Exposure to Synthetic Estrogens in Female Offspring.** See Cancer, June 3.

August 6-8—**Comprehensive Laparoscopy.** UCSD at Sea Lodge, San Diego. Saturday-Monday.

November 10-12—**Medical Complications of Obstetrics and Gynecology—Annual Fall Seminar in Obstetrics and Gynecology.** UCSF. Thursday-Saturday.

November 12-19—**Workshops in High Risk Pregnancy: Infertility.** UCSF at Royal Lahania Hotel, Maui, Hawaii. One week.

PEDIATRICS

May 16-18—**Psychological Aspects of Juvenile Diabetes.** See Psychiatry, May 16-18.

May 18—**Atherosclerosis and Diet: A Practical Pediatric Approach.** See Medicine, May 18.

May 30-June 1—**General Pediatrics—Annual Spring Meeting.** American Academy of Pediatrics, Northern Calif. Chapter 1, at Hyatt House, Monterey. Monday-Wednesday. 9 hrs. $100. Contact: Mrs. Helen Olson, Asst. Sec., AAP, No. Calif. Chapter 1, 2709 Calhoun St., Alameda 94501. (415) 522-8934.

June 17—**Conference on Prematurity—16th Annual.** STAN. Friday. Contact: Philip Sunshine, MD, Dept. of Pediatrics, Stanford Univ. Sch. of Med., Stanford 94305.

June 22-24—**Pediatric Gastroenterology.** UCSF. Wednesday-Friday.

September 14-16—**Pediatric Dermatology.** See Medicine, September 14-16.

September 15-16—**Pediatric Urology.** See Surgery, September 15-16.

October 6-7—**Pediatric Nephrology.** See Medicine, October 6-7.

October 15-22—**Pediatrics for the Practitioner.** Children's Hospital of Long Beach and American Academy of Pediatrics, Chapter 2, at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. Contact: Margaret Frederick, Exec. Sec., Center for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

October 21-22—**Adolescent Sexuality and Related Problems.** UCD at Red Lion Motor Inn, Sacramento. Friday-Saturday.

November 4-5—**Children's Experiences of Health and Illness.** UCD at Claremont Hotel, Berkeley. Friday-Saturday.

November 7-11—**Pediatric Allergy and Clinical Immunology.** See Medicine, November 7-11.

PSYCHIATRY

May 15-18—**New Therapeutic Approaches with Biofeedback.** UCLA at Biltmore Hotel, Santa Barbara. Sunday-Wednesday.

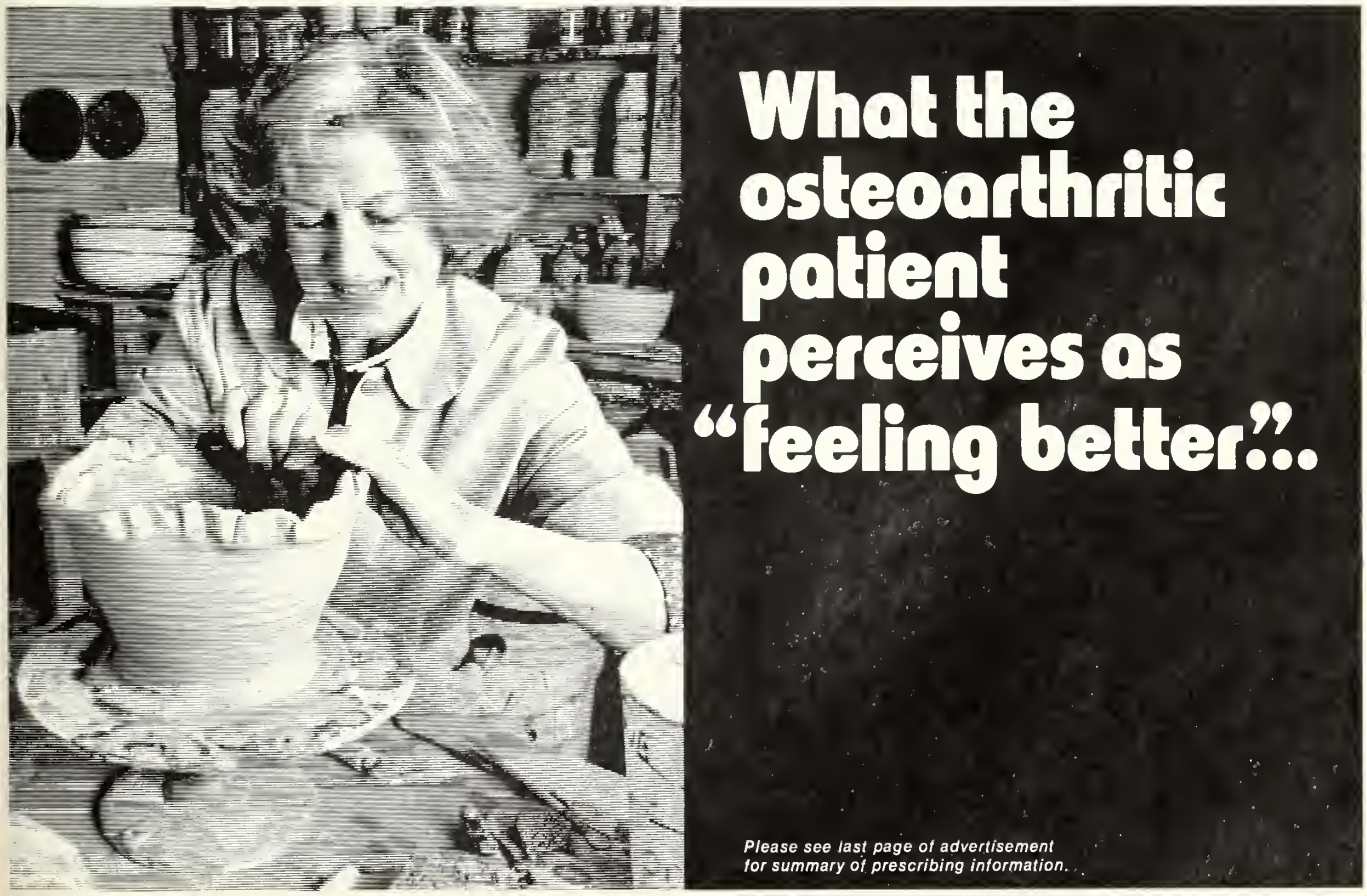
May 16-18—**Psychological Aspects of Juvenile Diabetes.** Diabetic Youth Foundation and American Diabetes Assn. at Bear Skin Meadow Camp. Monday-Wednesday. Contact: Diabetic Youth Foundation, 1128 Irvin St., San Francisco 94122. (415) 731-5113.

May 19-22—**Clinical Hypnosis—Introductory and Advanced Course.** See Of Interest To All, May 19-22.

June 2-4—**Psychosocial Care of the Dying Patient.** UCSF. Thursday-Saturday.

June 17-19—**Madness and Social Policy.** Mental Research Institute at Cabana Hyatt House, Palo Alto. Friday-Sunday. $75. Contact: Ms. L. Sheffet-Keys, MRI, 555 Middlefield Rd., Palo Alto 94301. (415) 321-3055.

June 27-July 1—**Comparative Psychiatric Therapies: The Diffi-**



cult to Treat Patient. USC at Vacation Village, San Diego. Monday-Friday. 21¼ hrs. $200.

November 14-18—**Group Therapy Seminars.** UCSF at Merritt Hotel, Oakland. Monday-Friday.

RADIOLOGY AND PATHOLOGY

June 3-5—**Spring Diagnostic Ultrasound Conference—2nd Annual.** Los Angeles Radiological Society at Century Plaza Hotel, Los Angeles. Friday-Sunday. Contact: Earl P. Detrick, MD, Westlake Community Hospital, 4415 Lakeview Canyon Rd., Westlake Village 91361.

June 18-25—**Lab Management for Pathologists.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week.

June 19-24—**Pathology of the Lung.** UCSD. Sunday-Friday.

September 14—**Diagnostic Radiology.** LLU. 4 hrs. $25.

September 17—**Radiology Symposium—5th Annual.** Southern Calif. Permanente Medical Group at Bonaventure Hotel, Los Angeles. Saturday. Contact: Shirley Gach, So. Calif. Permanente Med. Grp., Education and Research Dept., 4900 Sunset Blvd., Los Angeles 90027. (213) 667-4241.

October 4-7—**Recent Advances in Diagnostic Radiology.** UCSD. Tuesday-Friday.

October 21-23—**Society of Nuclear Medicine—2nd Annual Western Regional Meeting.** Aladdin Hotel, Las Vegas. Friday-Sunday. Contact: Justine J. Lynch, P.O. Box 40279, San Francisco 94140. (415) 647-0722 or (415) 647-5909.

Postgraduate Videotape Programs in Diagnostic Radiology. Developed by Dept. of Radiology, UCSF. 15 programs in all aspects of diagnostic radiology. Outstanding group of national and international guest lecturers in addition to UC staff present basic approaches to radiographic interpretation and technique as well as new research and clinical advances. Contact: Aveleen Blumenstock, Videotape Coordinator, Dept. of Radiology, UCSF, San Francisco 94143. (415) 666-1988.

SURGERY AND ANESTHESIOLOGY

May 15-19—**Fifteenth Biennial Western Conference on Anesthesiology.** Hyatt Regency Hotel, San Francisco. Sunday-Thursday. 18 hrs. $100. Contact: Exec. Sec., BWCA, 707-2525 Willow St., Vancouver, B.C., Canada V5Z 3N8.

May 19-20—**Phaco-Fragmentation.** UCSF. Thursday-Friday.

May 19-21—**Neurosurgery—7th Annual Course.** UCSF at Hyatt on Union Square, San Francisco. Thursday-Saturday.

May 20-21—**Anesthesiology Refresher Course.** Biennial Western Conference on Anesthesiology at Del Monte Hyatt House, Monterey. Friday-Saturday. 8¼ hrs. $50. Contact: Exec. Sec., BWCA, 707-2525 Willow St., Vancouver, B.C., Canada V5Z 3N8.

May 26-28—**Retina Workshop.** Retina Research Fund of St. Mary's Hospital and Medical Center, San Francisco, at Quail Lodge, Carmel Valley. Thursday-Saturday. 12 hrs. $135. Contact: Ms. Claire Ohiyon, c/o Howard Schatz, MD, 3637 Sacramento St., San Francisco 94118. (415) 921-4860.

June 3-4—**Ophthalmology Update II.** PMC at Golden Gateway Holiday Inn, San Francisco. Friday-Saturday.

June 9-10—**Trauma.** UCSF at Mary's Help Hospital, Daly City. Thursday-Friday.

June 9-12—**California Society of Anesthesiologists—Annual Scientific Meeting.** Town and Country Hotel, San Diego. Thursday-Sunday. Contact: CSA, 100 S. Ellsworth Ave., Suite 806, San Mateo 94401.

June 10-12—**Modern Laryngoscopy and Bronchoesophagoscopy: A Theoretical and Practical Course.** UCLA. Friday-Sunday. Contact: Paul H. Ward, MD, Div. of Head and Neck Surgery, UCLA Sch. of Med., Los Angeles 90024.

June 16-17—**The Neck and Upper Extremity in Sports.** USC at Airport Park Hotel, Inglewood. Thursday-Friday. 13 hrs. $105.

June 16-18—**Highlights of Ophthalmology.** PMC. Thursday-Saturday.

June 18-19—**American Association for Study of Headache.** See Of Interest To All, June 18-19.

July 2-9—**Manipulation, Mobilization and Related Techniques in Treatment of Musculo-Skeletal and Myofascial Pain Syndromes.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. $275.

August 6—**Intensive Care—Fifth Saturday Symposium.** See Of Interest To All, August 6.

August 6-13—**Ophthalmology.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week.

August 13-14—**Clinical Relevance of Recent Advances in Anesthesia: The Critically Ill Child and Adult.** STAN. Saturday-Sunday. 14 hours. Contact: Janie Sydow, Dept. of Anesthesiology, Stanford Univ. School of Medicine, Stanford 94305. (415) 497-6238.

September 9-10—**Trauma.** UCSF at Mary's Help Hospital, Daly City. Friday-Saturday.

September 9-10—**Vascular Surgery.** UCSF. Friday-Saturday.

September 15-16—**Pediatric Urology.** UCD at Hyatt Lake Tahoe. Thursday-Friday. 10 hrs. $150.

October 10-14—**Congress of Neurological Surgeons.** Hilton Hotel, San Francisco. Monday-Friday. 40 hrs. $75, members; $100, nonmembers. Contact: David L. Kelly, Jr., MD, Bowman Gray School of Medicine, Winston-Salem, NC 27103. (919) 727-4653.

October 28-29—**The Macula.** Retina Research Fund of St. Mary's Hospital and Medical Center at Hyatt on Union Square, San Francisco. Friday-Saturday. Contact: Claire Ohiyon, c/o Howard Schatz, MD, 3637 Sacramento St., San Francisco 94118. (415) 921-4860.

October 30-November 4—**American Society of Plastic and Reconstructive Surgeons—Annual Convention.** Hilton Hotel, San Francisco. Sunday-Friday. 33 hrs. Contact: Linda Campbell, ASPRS, 29 E. Madison St., Chicago 60602. (312) 641-0593.

November 12—**Current Concepts in Ophthalmic Plastic Surgery.** Jules Stein Eye Institute, Los Angeles. Saturday. Contact: Shelley E. Reid, Jules Stein Eye Institute, UCLA Sch. of Med., Ctr. for the Health Sciences, Los Angeles 90024.

November 19-20—**American Society of Anesthesiologists—Regional Refresher Course.** Sahara Hotel, Lake Tahoe. Saturday-Sunday. Contact: ASA, 515 Busse Highway, Park Ridge, IL 60068.

December 7-9—**Annual Ophthalmology Program.** UCSF. Wednesday-Friday.

December 14—**Treatment of Parkinsonism and Modern Concepts.** LLU. Wednesday. 4 hrs. $25.

Orthopaedic Audio-Synopsis Foundation. A non-profit service for Orthopaedic Surgeons publishing monthly recorded teaching programs which include summaries of pertinent literature and excerpts from national and international orthopaedic meetings. Monthly c-60 cassette tapes. Annual subscription rate $75 ($37.50 for residents). Contact: A. Harris, Man. Ed., OASF, 1510 Oxley St., So. Pasadena 91030. (213) 682-1760.

OF INTEREST TO ALL PHYSICIANS

May 16-20—**Postgraduate Institute for Emergency Physicians, Symposium I.** UCSD at Sheraton Harbor Island Hotel, San Diego. Monday-Friday.

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May 16-22—**Diving Medicine.** UCSF at VA Hospital, Fresno. Monday-Sunday.

May 19-21—**Ambulatory Monitoring.** Medical Communications and Services Assn., STAN and Stanford Research Institute at Fairmont Hotel, San Francisco. Thursday-Saturday. 14 hrs. $100. Contact: Nancy Jacobsen, MCSA, 1107 N.E. 45th St., Rm. 315, Seattle, WA 98105. (206) 633-0505.

May 19-22—**Clinical Hypnosis—Introductory and Advanced Course.** American Society of Clinical Hypnosis at San Francisco. Thursday-Sunday. 25 hrs. $225. Contact: William F. Hoffman, Jr., Exec. Sec., ASCH, Education and Research Foundation, 2400 E Devon Ave., Suite 218, Des Plaines, ILL 60018. (312) 297-3317.

May 21-22—**Family Practice Management of Ischemic Heart Disease.** UCLA. Saturday-Sunday.

May 22-27—**Fingers-to-the-Toes—An Orthopedic Approach for the General Practitioner.** UCD at Stanford Sierra Camp, Fallen Leaf Lake. Sunday-Friday.

May 25-27—**Pain: Diagnosis and Management.** UCLA. Wednesday-Friday.

May 26-30—**Patient Oriented Applied Medical Advances.** UCSF at Hawaii. Thursday-Monday.

June 2-4—**Psychosocial Care of the Dying Patient.** See Psychiatry, June 2-4.

June 8-12—**California Chapter, American College of Emergency Physicians—Scientific Assembly.** Fairmont Hotel, San Francisco. Wednesday-Sunday. Contact: Calif. Chapter, ACEP, 58 California Ave., Orinda 94563.

June 9-11—**Management of Medical Problems.** PMC. Thursday-Saturday.

June 9-11—**Nutritional Care of the Hospitalized Patient.** UCSF at Hyatt Regency Hotel, San Francisco. Thursday-Saturday. 16 hrs. $175.

June 10-11—**Clinical Application of Hyperbaric Oxygen.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Friday-Saturday. $150. Contact: Exec. Sec., Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

June 16-17—**The Neck and Upper Extremity in Sports.** See Surgery, June 16-17

June 18-19—**American Association for Study of Headache—Annual Meeting.** Hyatt on Union Square, San Francisco. Saturday-Sunday. Contact: Seymour Diamond, MD, Exec. Sec., Am. Assn. for Study of Headache, 5252 N. Western Ave., Chicago 60625. (312) 878-5558.

June 18-22—**American Medical Association—126th Annual Convention.** Fairmont Hotel, San Francisco. Saturday-Wednesday. Contact: AMA, 535 N. Dearborn St., Chicago 60610.

June 21-22—**Pain Clinics.** UC-Berkeley Extension and Vallejo General Hospital at University of Calif., Berkeley. Tuesday-Wednesday. $50. Contact: UC Extension, 2223 Fulton St., Berkeley 94720. (415) 642-1064.

July 8-10, 15-17—**Introduction to Sex Counseling Principles.** UCSF Human Sexuality Program at UCSF. Two weekends. 50 hrs. $175, per person; $300, per couple. Contact: Susan Hansen, Human Sexuality Program, 350 Parnassus Ave., Suite 700, San Francisco 94143. (415) 666-4787.

July 11-15—**Postgraduate Institute for Emergency Physicians, Symposium III.** UCSD at Hilton Hotel, San Diego. Monday-Friday.

July 13—**Problems in Acid Base Balance.** LLU. Wednesday. 4 hrs. $25.

July 31-August 5—**National Medical Association—82nd Annual Scientific Assembly.** Bonaventure Hotel, Los Angeles. Sunday-Friday. Contact: Alfred F. Fisher, Exec. Dir., NMA, 1625 Eye St., NW, Suite 725A, Washington, D.C. 20006.

August 6—**Intensive Care—Fifth Saturday Symposium.** Mercy Hospital and Medical Center, San Diego. Saturday. 8 hrs. Contact: Gilbert E. Kinyon, MD, Dir. of Anesthesia and Respiratory Therapy, Mercy Hosp. and Med. Ctr., 4077 Fifth Ave., San Diego 92103. (714) 294-8037.

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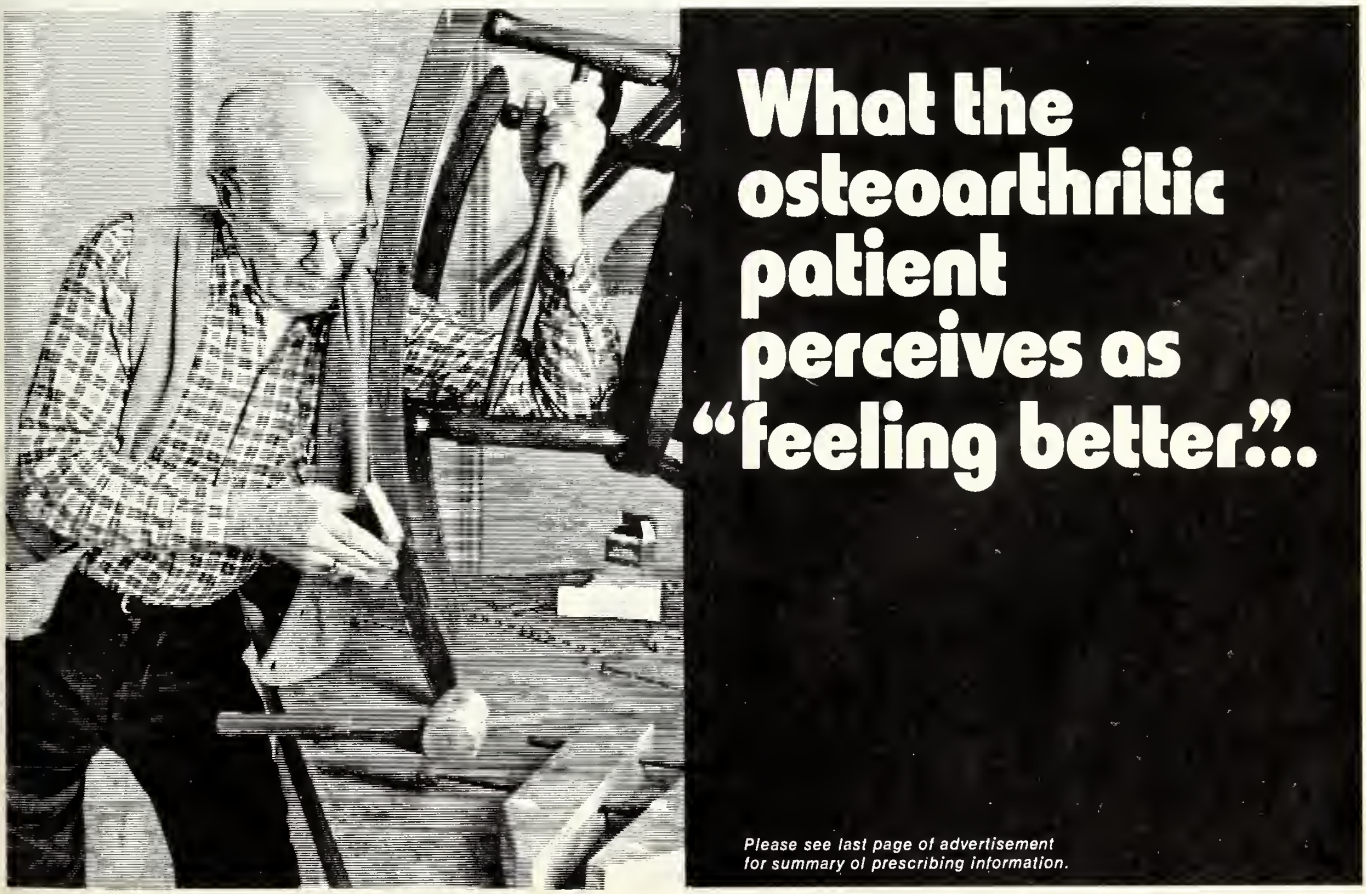

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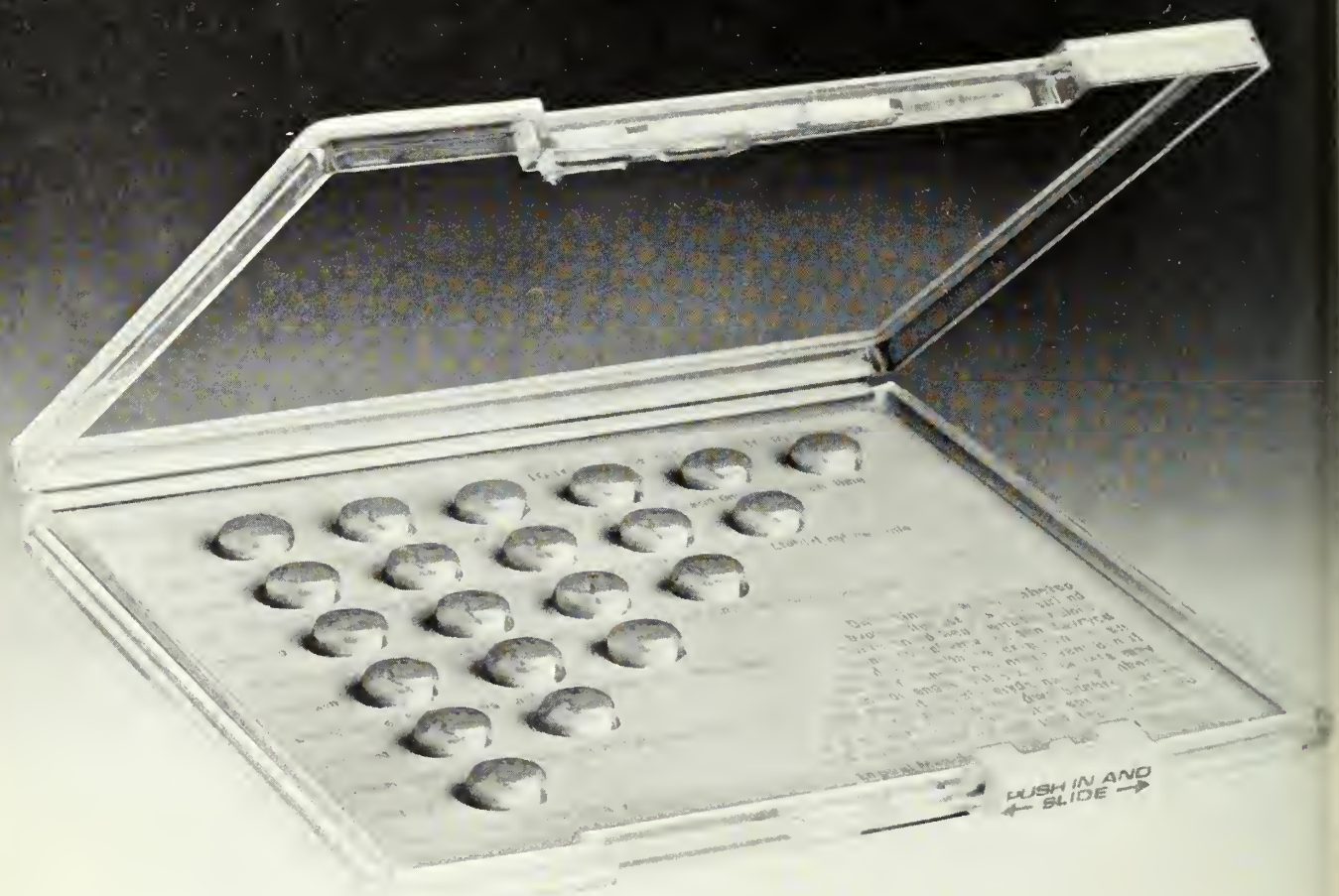

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August 13-24—**Postgraduate Refresher Course—20th Annual.** USC at Hawaii. 11 days. 37 hrs.

August 15-19—**Postgraduate Institute for Emergency Physicians, Symposium II.** UCSD at Islandia Hotel, San Diego. Sunday-Thursday.

August 22-27—**Family Practice Refresher Course—5th Annual.** UCD at Del Monte Hyatt House, Monterey. Monday-Saturday. 30 hrs. $225.

August 30-October 18—**Evening Lectures in Medicine.** UCSF at Oakland Hospital, Oakland. Tuesday evenings.

September 19-23—**Topics in Emergency Medicine—Postgraduate Course for Career Emergency Physicians.** UCSF at Ralph K. Davies Medical Center, San Francisco. Monday-Friday. 40 hrs. $300.

September 25-30—**Postgraduate Institute for Emergency Physicians, Symposium I.** UCSD at Town and Country Hotel, San Diego. Sunday-Friday.

October 3-7—**Primary Care.** STAN. Monday-Friday.

October 6-9—**Clinical Pharmacology.** UCSF at Hilo, Hawaii. Thursday-Saturday.

October 12—**Pain and Its Management.** LLU. Wednesday. 4 hrs. $25.

October 12-14—**Alcoholism Course for Primary Care Physicians.** UCSD at Town and Country Hotel, San Diego. Wednesday-Friday.

October 14-16, 21-23—**Introduction to Sex Counseling Principles.** UCSF Human Sexuality Program at UCSF. Two weekends. 50 hrs. $175, per person; $300, per couple. Contact: Susan Hansen, Human Sexuality Program, 350 Parnassus, Suite 700, San Francisco 94143. (415) 666-4787.

October 17-21—**Family Practice Review—2nd Annual.** LLU. Monday-Friday. 30 hrs. $150.

October 20-21—**Geriatrics.** UCSF at Veteran's Home of California, Yountville. Thursday-Friday.

October 24-28—**Postgraduate Institute for Emergency Physicians, Symposium III.** UCSD at Vacation Village, San Diego. Monday-Friday.

October 30-November 3—**American Medical Association—Regional Meeting.** Sheraton Waikiki, Honolulu, Hawaii. Sunday-Thursday. Contact: AMA, 535 N. Dearborn, Chicago 60610.

October 31-November 4—**Intensive Care.** STAN. Monday-Friday.

November 10-11—**Emergency Medicine (Advanced Course).** UCSF. Thursday-Friday.

December 12-16—**Postgraduate Institute for Emergency Physicians, Symposium II.** UCSD at Islandia Hotel, San Diego. Monday-Friday.

December 14—**Treatment of Parkinsonism.** See Surgery, December 14.

Audio-Digest Foundation. A non-profit subsidiary of CMA. Twice-a-month tape recorded summaries of leading national meetings and surveys of current literature. Services by subscription in: Family Practice, Surgery, Internal Medicine, Ob/Gyn, Pediatrics, Psychiatry, Anesthesiology, Ophthalmology, Otorhinolaryngology. Catalog of lectures and panel discussions in all areas of medical practice also available. $90 per year. Also available are ACOG Audio Education Courses, edited and produced by Audio-Digest Foundation —32, 6- and 3-hour cassette courses available including: Family Life and Sexual Counseling; Medical Complications of Pregnancy; Gynecological Endocrinology; Psychosomatic Ob/Gyn; Immunology in Ob/Gyn; and Pediatric and Adolescent Gyn. Available soon: Cassette albums of State of the Art Lectures and Workshops from 1976 American College of Physicians meeting and Postgraduate Courses from 1976 American Psychiatric Association meeting. Contact: Mr. Claron L. Oakley, Editor, 1577 E. Chevy Chase Dr., Glendale 91206.

(Continued on Page 41)

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The relief of pain and stiffness in patients with osteoarthritis

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consider the effect on coexisting diabetes when you prescribe a vasodilator*

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no interference in the management of the diabetic patient has been reported with

VASODILAN®
(ISOXSUPRINE HCl)
the compatible vasodilator

TABLETS, 20 mg.

*Indications: Based on a review of this drug by the National Academy of Sciences-National Research Council and/or other information, the FDA has classified the indications as follows:

Possibly Effective:

1. For the relief of symptoms associated with cerebral vascular insufficiency.
2. In peripheral vascular disease of arteriosclerosis obliterans, thromboangiitis obliterans (Buerger's Disease) and Raynaud's disease.

Final classification of the less-than-effective indications requires further investigation.

Composition: Vasodilan tablets, isoxsuprine HCl, 10 mg. and 20 mg. Vasodilan injection, isoxsuprine HCl, 5 mg., per ml.

Dosage and Administration: Oral: 10 to 20 mg., three or four times daily.

Intramuscular: 5 to 10 mg. (1 or 2 ml.) two or three times daily. Intramuscular administration may be used initially in severe or acute conditions.

Contraindications and Cautions: There are no known contraindications to oral use when administered in recommended doses. Should not be given immediately postpartum or in the presence of arterial bleeding.

Parenteral administration is not recommended in the presence of hypotension or tachycardia.

Intravenous administration should not be given because of increased likelihood of side effects.

Adverse Reactions: On rare occasions oral administration of the drug has been associated in time with the occurrence of hypotension, tachycardia, nausea, vomiting, dizziness, abdominal distress, and severe rash. If rash appears the drug should be discontinued.

Although available evidence suggests a temporal association of these reactions with isoxsuprine, a causal relationship can be neither confirmed nor refuted.

Administration of single dose of 10 mg. intramuscularly may result in hypotension and tachycardia. These symptoms are more pronounced in higher doses. For these reasons single intramuscular doses exceeding 10 mg. are not recommended. Repeated administration of 5 to 10 mg. intramuscularly at suitable intervals may be employed.

Supplied: Tablets, 10 mg., bottles of 100, 1000, 5000 and Unit Dose; Tablets, 20 mg., bottles of 100, 500, 1000, 5000 and Unit Dose; Injection, 10 mg. per 2 ml. ampul, box of six 2 ml. ampuls.

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(Continued from Page 39)

PRECEPTORSHIPS AND TRAINEESHIPS

Training for Physicians in General Internal Medicine. LLU. Four weeks or more, by arrangement. Bedside and classroom training, practical aspects of clinical care and management. 160 hrs. Contact: John E. Peterson, MD, LLU.

Training of Physicians in Modern Concepts of Pulmonary Care. LLU. Four weeks or more, by arrangement. Diagnostic and therapeutic methods in medical chest disease, physiological methodology of modern pulmonary care programs, use of new instrumentation in the field. 160 hrs. Contact: John E. Hodgkin, MD, Chief, Section of Medical Chest Diseases, LLU.

Physician-in-Residence Preceptorship in Pulmonary Disease. USC, Pulmonary Disease Section, Dept. of Medicine and Postgraduate Medical Education. One month or more, by arrangement. Opportunity for practicing physician to achieve specified knowledge and skills in adult pulmonary medicine. Contact: Oscar J. Balchum, MD, PhD, USC.

Training for Physicians in Nephrology. LLU. Four weeks or more, by arrangement. Hemodialysis, peritoneal dialysis, renal biopsy, and kidney transplantation. 160 hrs. Contact: Robert E. Soderblom, MD, LLU.

Preceptorships in Cardiology. PMC. By arrangement. $200 per mo.; $500 for 3 mos. Contact: Arthur Selzer, MD, PMC.

Preceptorships in Practical Office Dermatology. PMC. Wednesdays or Fridays, 9:00 a.m.-12:00 noon, for 10 weeks. Periods begin Oct., Jan., or April. $100. Contact: Harold M. Schneidman, MD, Dept. of Dermatology, PMC.

Preceptorships in Infectious Disease. PMC. Full time for four weeks. To be arranged. $250. Contact: Rodney J. Valentine, MD, Chief, Div. of Infectious Diseases, PMC.

Preceptorships in Basic Sciences, Biochemistry and Biophysics, Dermatology, Echocardiography, International Health, Microbiology, Neurological Surgery, Obstetrics and Gynecology, Pediatrics, Pharmacology and Experimental Therapeutics, Physiology, Psychiatry, Urology. UCSF. By special arrangement.

Traineeships in Renal Dialysis. UCSF. By special arrangement.

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COUNCIL ON MEDICAL EDUCATION

THIS BULLETIN of information regarding continuing education programs and meetings of various medical organizations in Oregon is supplied by the Council on Medical Education of the Oregon Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Council on Medical Education, Oregon Medical Association, 5210 SW Corbett Ave., Portland, OR 97201; or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

University of Oregon Medical School, Department of Internal Medicine, 3181 SW Sam Jackson Park Road, Portland 97201:

Every Tuesday, 8:00 a.m. to 9:00 a.m.—**Internal Medicine Grand Rounds.** Library Auditorium, University of Oregon Health Sciences Center, Portland. Contact: Stephen R. Jones, MD, Department of Internal Medicine, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, 97201.

Providence Medical Center, 700 NE 47th Avenue, Portland 97213:

Every Wednesday, 8:00 a.m. in the auditorium—**Spring Medical Grand Rounds,** Providence Medical Center. Contact: David N. Gilbert, MD, Director of Medical Education, Providence Medical Center, 700 NE 47th, Portland 97213.

(Continued on Page 44)

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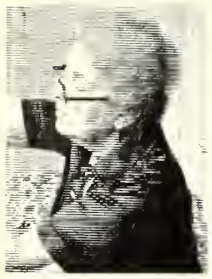
Please see last page of advertisement for summary of prescribing information



Nalfon®
fenoprofen calcium

Indications and Usage: Nalfon is indicated for relief of the signs and symptoms of rheumatoid arthritis and osteoarthritis It is indicated in the treatment of acute flares and exacerbations and in the long-term management of these diseases The safety and effectiveness of Nalfon have not been established in those rheumatoid arthritis patients who are designated by the American Rheumatism Association as Functional Class IV (largely or wholly incapacitated with patient bedridden or confined to wheelchair, permitting little or no self-care)

Contraindications: Nalfon is contraindicated in patients who have shown hypersensitivity to it

Because the potential exists for cross-sensitivity to aspirin and other nonsteroidal, anti-inflammatory drugs, Nalfon should not be given to patients in whom aspirin and other nonsteroidal, anti-inflammatory drugs induce the symptoms of asthma, rhinitis, or urticaria

Warnings: Nalfon should be given under close supervision to patients with a history of upper-gastrointestinal-tract disease and only after the Adverse Reactions section has been consulted Gastrointestinal bleeding, sometimes severe, has been reported in patients receiving Nalfon

In patients with active rheumatoid arthritis or osteoarthritis who also have an active peptic ulcer, attempts should be made to treat the arthritis with nonulcerogenic drugs If Nalfon must be given, the patient should be under close supervision for signs of ulcer perforation or severe gastrointestinal bleeding

In subacute and chronic studies in rats, Nalfon caused interstitial nephritis, glomerulonephritis, and renal papillary necrosis These abnormalities were dose related and began to appear at doses approximating the human dose In chronic studies in monkeys, interstitial nephritis also occurred following administration of Nalfon Although this was seen at doses considerably above the human dose, lower doses were not studied in this species During the course of the clinical trials, one patient developed bilateral suppurative pyelonephritis, underwent laparotomy, went on to renal failure, and died with a diagnosis of septicemia and renal papillary necrosis It is not known whether these events were drug related A few patients developed mild elevations of the BUN during therapy with Nalfon Since Nalfon is eliminated primarily by the kidney, the drug should not be administered to patients with significantly impaired renal function It is desirable to perform periodic renal function tests in all patients receiving Nalfon

Precautions: In chronic studies in rats, high doses of Nalfon caused elevation of serum transaminase and hepatocellular hypertrophy In clinical trials, some patients developed elevation of serum transaminase, LDH, and alkaline phosphatase which persisted for some months and usually, but not always, declined despite continuation of the drug The significance of this is unknown It is recommended that periodic liver function tests be performed in patients receiving Nalfon and that the drug be discontinued if abnormalities occur.

The safety of this drug in pregnancy and lactation has not been established, and its use during these events is, therefore, not recommended Reproduction studies have been performed in rats and rabbits When fenoprofen was given to rats during pregnancy and continued to the time of labor, parturition was prolonged Similar results have been found with other nonsteroidal, anti-inflammatory drugs which inhibit prostaglandin synthetase

In-vitro studies have shown that fenoprofen, because of its affinity for albumin, may displace from their binding sites other drugs which are also albumin bound, and this may lead to drug interaction Theoretically, fenoprofen, as well as other nonsteroidal, anti-inflammatory agents, could likewise be displaced Patients receiving hydantoin, sulfonamides, or sulfonylureas should be observed for signs of toxicity to these drugs In patients receiving coumarin-type anticoagulants, the addition of Nalfon to therapy could prolong the prothrombin time Patients receiving both drugs should be under careful observation

In patients receiving Nalfon® (fenoprofen calcium, Dista) and steroid concomitantly, any reduction of steroid dose should be gradual to avoid the possible complications of sudden steroid withdrawal

Patients with initial low hemoglobin values who are receiving long-term therapy with Nalfon should have a hemoglobin determination at reasonable intervals.

Peripheral edema has been observed in some patients taking Nalfon, therefore, Nalfon should be used with caution in patients with compromised cardiac function

Studies to date have not shown changes in the eye attributed to administration of Nalfon However, because of adverse eye findings in animal studies with some other nonsteroidal, anti-inflammatory drugs, it is recommended that ophthalmologic studies be carried out within a reasonable period of time after chronic therapy with Nalfon has been started and at periodic intervals thereafter

Since food decreases the blood levels of Nalfon, the drug should be given thirty minutes before or two hours after meals during the daytime

When phenobarbital, which may enhance the metabolism of Nalfon, is added or withdrawn, dosage adjustment of Nalfon may be required

Caution should be exercised by patients whose activities require alertness if they experience central-nervous-system side-effects from Nalfon

Since the safety of Nalfon in patients with impaired hearing has not been established, these patients should have periodic tests of auditory function during chronic therapy with Nalfon

Nalfon decreases platelet aggregation and may prolong bleeding time. Patients who may be adversely affected by prolongation of the bleeding time should be carefully observed when Nalfon is administered

Adverse Reactions: *Digestive System*—The most common type of adverse reaction concerned the gastrointestinal system Dyspepsia occurred most frequently, being observed in about one out of seven patients Other adverse reactions, in descending order of frequency, were constipation, nausea, vomiting, abdominal pain, anorexia, occult blood in the stool, diarrhea, flatulence, and dry mouth.

Three instances of peptic ulceration and/or gastrointestinal hemorrhage that may have been due to the drug and four instances in which drug relationship was questionable were observed in 3,391 individuals to whom the drug was administered for periods of time ranging up to 165 weeks

In less than 2 percent of patients, the drug was discontinued because of adverse gastrointestinal reactions.

Skin and Appendages—The most common adverse effect was pruritus, which was seen in about one out of ten patients Other adverse reactions were rash, increased sweating, and urticaria

In about 1 percent of patients, Nalfon was discontinued because of an adverse effect related to the skin

Nervous System—The most frequent adverse reaction observed was somnolence, which occurred in about one out of seven patients Other adverse effects, which occurred less frequently, were dizziness, tremor, confusion, and insomnia

Nalfon was discontinued in less than 0 2 percent of patients because of these side-effects

Special Senses—The most common adverse reaction was tinnitus, which was seen in about one out of ten patients Other reactions observed, in descending order of frequency, were blurred vision and decreased hearing

In about 0 2 percent of patients, Nalfon was discontinued owing to adverse effects related to the special senses

Cardiovascular—The most frequent adverse effect observed was palpitations This was noted in about one out of twenty-five patients Tachycardia was observed less frequently

In less than 0.5 percent of patients, Nalfon was discontinued as a result of cardiovascular adverse reactions

Laboratory—Anemia was noted in about one out of 500 patients Therapy with Nalfon had to be discontinued in one patient because of anemia Increase in alkaline phosphatase, LDH, and SGOT was observed (see Precautions)

Miscellaneous—Headache was seen in about one out of seven patients Less frequently observed, in descending order of frequency, were nervousness, asthenia, dyspnea, peripheral edema, fatigue, malaise, and dysuria [031677]

Additional information available to the profession on request

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University of Oregon Medical School, Infectious Disease Conferences, 3181 SW Sam Jackson Park Road, Portland.
Every Thursday, 12:00 Noon—**Infectious Disease Conference** (through June 2), Room 8B-60 UHS (University Hospital South).

FAMILY PRACTICE

Every Wednesday, 11:00 a.m. to 12:00 Noon. **Family Practice Grand Rounds.** Family Practice Center, University of Oregon Health Sciences Center. Contact: William A. Fisher, MD, University of Oregon Health Sciences Center, Department of Family Practice, 3181 SW Sam Jackson Park Road, Portland 97201.

May 19—**Woodland Park Hospital Family Practice Symposium.** Main Auditorium, Woodland Park Hospital. Contact: Robert T. Childs, MD, 10300 NE Hancock Street, Portland 97220.

INTERNAL MEDICINE

Every Tuesday, 8:00 a.m. to 9:00 a.m.—**Internal Medicine Grand Rounds.** Library Auditorium, University of Oregon Health Sciences Center, Portland. Contact: Stephen Jones, MD, Department of Internal Medicine, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland 97201.

OF INTEREST TO ALL PHYSICIANS

May 20-22—**Sports Medicine Course.** Oregon State University, Corvallis. Contact: Dr. Steven Roy, Oregon State University, Student Health Center, Corvallis 97330.

WASHINGTON, ALASKA, MONTANA AND IDAHO

In order to have future activities listed here or to receive information on these and other activities, please write Ms. Joan M. Kelday, Information Specialist, Continuing Medical Education, WAMI Program, University of Washington School of Medicine, Health Sciences Building, SC-64, Seattle, Washington 98195. Phone: (206) 543-6995.

May 18—**Evaluation of Acute Trauma.** Wednesday. Univ. of Wash. in Anacortes, Wash. 7:30-10 a.m., Island Hospital. 2½ hrs. Contact: Harry Eiesland, MD, 24th and M Ave., Anacortes, WA 98221. (206) 292-3101.

May 19-20—**Fluid Electrolyte Disorders: A Clinical Approach.** Thursday-Friday. Virginia Mason Medical Center Auditorium, Seattle. Hours and fee to be determined. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) 223-6898.

May 20-21—**Coronary Bypass Surgery.** Friday-Saturday. Seattle. Contact: Pat Lind, Div. of CME, HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle, WA 98195. (206) 543-9495.

May 23-27—**University of Washington Circuit Course on Management of Pain.** Monday, May 23, Great Falls, Mont., Billings, Mont.; Wednesday, May 25, Bozeman, Mont.; Thursday, May 26, Missoula, Mont.; Friday, May 27, Kalispell, Mont. 4 hrs. MDs, $25; others, $15. Contact: Div. of CME, HSB, SC-500, Univ. of Wash. Sch. of Med., Seattle, WA 98195. (206) 543-9495.

May 23—**Internal Medicine Review: Medical Genetics.** Monday. Univ. of Wash. in Wenatchee, Wash. 7-9 p.m., Wenatchee Valley Clinic. 2 hrs. Contact: William M. McKee, MD, PO Box 489, Wenatchee, WA 98801. (509) 663-8711.

May 24—**Internal Medicine Review: Medical Genetics.** Tuesday. Univ. of Wash. in Yakima, Wash. 5-7 p.m., Memorial Hospital. 2 hrs. Contact: Harry Kimball, MD, Yakima Medical Center, Yakima, WA 98902. (509) 248-6791.

May 26—**Internal Medicine Review: Radiologic Aspects of Internal Disease.** Thursday. Univ. of Wash. in Billings, Mont. 7-9:30 a.m., Marillac Hall. 2½ hrs. Contact: Mrs. Frances Burt, Cont. Med. Ed., Marillac Hall, Billings, MT 59101. (406) 252-2121, Ext. 258.

May 27—**Internal Medicine Review: Radiologic Aspects of Internal Disease.** Friday. Univ. of Wash. in Missoula, Mont. 8:30-11 a.m., St. Patrick Hospital. 2½ hrs. Contact: James E. Gouaux, MD, 515 Kensington, Missoula, MT 59801. (406) 549-4581.

June 3-4—**Ophthalmology for the Non-Ophthalmologist.** Friday-Saturday. Virginia Mason Medical Center Auditorium, Seattle. Hours and fee to be determined. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) 223-6898.

June 17-18—**Mountaineering Medicine.** Friday-Saturday. Virginia Mason Medical Center Auditorium, Seattle. Hours and fee to be determined. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) 223-6898.

August 29-September 2—**American College of Physicians MKSAP Course.** Monday-Friday. Health Sciences Auditorium, Univ. of Wash., Seattle. 36 hrs. Members, $140; ACP Associates, $70; non-member physicians, $200; residents, research fellows, $140. Contact: American College of Physicians, 4200 Pine St., Philadelphia, PA 19104. (215) 243-1200 or Division of Cont. Med. Ed., SC-64, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-9495.

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Her next attack of cystitis may require

the Bactrim 3-system

1. In the urinary tract

Highly effective with fewer recurrences compared to ampicillin or cephalexin

Bactrim has shown high effectiveness not only against *Escherichia coli*, the major uropathogen, but also against most other *Enterobacteriaceae* involved in recurrent UTI. Substantially fewer recurrences have been recorded with Bactrim, as compared to ampicillin or cephalexin.*

Results one month after cessation of treatment

	No. of patients	Antimicrobial therapy	% Negative cultures†
Study 1	80	10-day Bactrim	71.3
	76	10-day ampicillin	56.6
Study 2	60	28-day cephalexin	56.7

Bactrim tablets were used. Bioequivalency studies show one Bactrim DS tablet to be equivalent to two regular strength Bactrim tablets.

*Data on file, Medical Department, Hoffmann-La Roche Inc.
†Criterion: 1000 or fewer organisms/ml urine.

2. In the vaginal tract

It appears from recent studies that the likelihood of recurrent UTI is enhanced by the establishment of large numbers of *E. coli* or other uropathogens on the vaginal introitus.

Bactrim combats uropathogens colonizing the vaginal introitus

Trimethoprim has the distinctive ability to diffuse into vaginal fluid in effective concentrations, thereby reducing or eliminating the number of pathogens in the vaginal introitus, from which they often migrate into the urethra. Bactrim acts to minimize this source of recurrent cystitis in the female.

ROCHE

counterattack

3. In the lower intestinal tract

By its selective action against *Enterobacteriaceae* in the bowel, Bactrim reduces the risk of introital colonization by fecal uropathogens.

Attacks colonic reservoir of uropathogens without significant effect on normal ecologic balance

Bactrim's wide spectrum makes it valuable against most gram-negative bacteria that cause UTI recurrences, yet Bactrim has *no* significant effect on other normal, necessary intestinal flora. Also, Bactrim has rarely been found to cause the intestinal discomfort or fungal overgrowth often associated with broad-spectrum antibiotics.

Bactrim™ DS Double Strength Tablets

Each tablet contains 160 mg trimethoprim and 800 mg sulfamethoxazole.

Just one tablet b.i.d.

To clear her infection* and combat reinfecting organisms

*Due to susceptible strains of *E. coli, Klebsiella-Enterobacter* and *Proteus mirabilis, vulgaris* and *morganii.*

Please see summary of product information on following page.

For recurrent attacks of urinary tract infection in women

the Bactrim 3-system counterattack

- Acts on pathogens at vaginal and lower intestinal sites, in addition to urinary tract; helps eliminate reservoirs of reinfecting organisms
- Antimicrobial synergism plus wide-spectrum effectiveness
- Low incidence of bacterial resistance
- Contraindicated during pregnancy and the nursing period; during therapy, maintain adequate fluid intake, perform CBC's and urinalyses with microscopic examination

Bactrim™ DS

Each tablet contains 160 mg trimethoprim and 800 mg sulfamethoxazole.

Double Strength Tablets

Just one tablet b.i.d. for 10 to 14 days

- Day-and-night action against uropathogens
- B.I.D. regimen encourages patient compliance
- Offers high effectiveness with economy

Bactrim™ Tablets

Each tablet contains 80 mg trimethoprim and 400 mg sulfamethoxazole.

Two tablets b.i.d. for 10 to 14 days

Before prescribing, please consult complete product information, a summary of which follows:

Indications and Usage: For the treatment of urinary tract infections due to susceptible strains of the following organisms: *Escherichia coli, Klebsiella-Enterobacter, Proteus mirabilis, Proteus vulgaris, Proteus morganii.* **It is recommended that initial episodes of uncomplicated urinary tract infections be treated with a single effective antibacterial agent rather than the combination.** *Note.* The increasing frequency of resistant organisms limits the usefulness of all antibacterials, especially in these urinary tract infections.

Also for the treatment of documented *Pneumocystis carinii* pneumonitis. To date, this drug has been tested only in patients 9 months to 16 years of age who were immunosuppressed by cancer therapy.

The recommended quantitative disc susceptibility method (*Federal Register, 37:*20527-20529, 1972) may be used to estimate bacterial susceptibility to Bactrim. A laboratory report of "Susceptible to trimethoprim-sulfamethoxazole" indicates an infection likely to respond to Bactrim therapy. If infection is confined to the urine, "Intermediate susceptibility" also indicates a likely response. "Resistant" indicates that response is unlikely.

Contraindications: Hypersensitivity to trimethoprim or sulfonamides; pregnancy, nursing mothers; infants less than two months of age.

Warnings: Deaths from hypersensitivity reactions, agranulocytosis, aplastic anemia and other blood dyscrasias have been associated with sulfonamides. Experience with trimethoprim is much more limited but occasional interference with hematopoiesis has been reported as well as an increased incidence of thrombopenia with purpura in elderly patients on certain diuretics, primarily thiazides. Sore throat, fever, pallor, purpura or jaundice may be early signs of serious blood disorders. Frequent CBC's are recommended; therapy should be discontinued if a significantly reduced count of any formed blood element is noted.

Precautions: Use cautiously in patients with impaired renal or hepatic function, possible folate deficiency, severe allergy or bronchial asthma. In patients with glucose-6-phosphate dehydrogenase deficiency, hemolysis, frequently dose-related, may occur. During therapy, maintain adequate fluid intake and perform frequent urinalyses, with careful microscopic examination, and renal function tests, particularly where there is impaired renal function.

Adverse Reactions: All major reactions to sulfonamides and trimethoprim are included, even if not reported with Bactrim. *Blood dyscrasias:* Agranulocytosis, aplastic anemia, megaloblastic anemia, thrombopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia. *Allergic reactions:* Erythema multiforme, Stevens-Johnson syndrome, generalized skin eruptions, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis. *Gastrointestinal reactions:* Glossitis, stomatitis, nausea, emesis, abdominal pains, hepatitis, diarrhea and pancreatitis. *CNS reactions:* Headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo, insomnia, apathy, fatigue, muscle weakness and nervousness. *Miscellaneous reactions:* Drug fever, chills, toxic nephrosis with oliguria and anuria, periarteritis nodosa and L.E. phenomenon. Due to certain chemical similarities to some goitrogens, diuretics (acetazolamide, thiazides) and oral hypoglycemic agents, sulfonamides have caused rare instances of goiter production, diuresis and hypoglycemia in patients; cross-sensitivity with these agents may exist. In rats, long-term therapy with sulfonamides has produced thyroid malignancies.

Dosage: Not recommended for infants less than two months of age. *Urinary tract infections.* Usual adult dosage—1 DS tablet (double strength), 2 tablets (single strength) or 4 teasp. (20 ml) b.i.d. for 10-14 days.

Recommended dosage for children—8 mg/kg trimethoprim and 40 mg/kg sulfamethoxazole per 24 hours, in two divided doses for 10 days. A guide follows:

Children two months of age or older.

Weight		Dose—every 12 hours	
lbs	kgs	Teaspoonfuls	Tablets
20	9	1 teasp. (5 ml)	½ tablet
40	18	2 teasp. (10 ml)	1 tablet
60	27	3 teasp. (15 ml)	1½ tablets
80	36	4 teasp. (20 ml)	2 tablets or 1 DS tablet

For patients with renal impairment.

Creatinine Clearance (ml/min)	Recommended Dosage Regimen
Above 30	Usual standard regimen
15-30	½ the usual regimen
Below 15	Use not recommended

Pneumocystis carinii pneumonitis. Recommended dosage: 20 mg/kg trimethoprim and 100 mg/kg sulfamethoxazole per 24 hours in equal doses every 6 hours for 14 days. See complete product information for suggested children's dosage table.

Supplied: *Double Strength (DS) tablets,* each containing 160 mg trimethoprim and 800 mg sulfamethoxazole, bottles of 100; Tel-E-Dose® packages of 100. *Tablets,* each containing 80 mg trimethoprim and 400 mg sulfamethoxazole—bottles of 100 and 500; Tel-E-Dose® packages of 100; Prescription Paks of 40, available singly and in trays of 10. *Oral suspension,* containing in each teaspoonful (5 ml) the equivalent of 40 mg trimethoprim and 200 mg sulfamethoxazole, fruit-licorice flavored—bottles of 16 oz (1 pint).

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DYAZIDE®

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Each capsule contains 50 mg. of Dyrenium® (triamterene, SK&F Co.) and 25 mg. of hydrochlorothiazide.

MAKES SENSE FOR LONG-TERM CONTROL OF HYPERTENSION*

Before prescribing, see complete prescribing information in SK&F Co. literature or PDR. A brief summary follows:

* WARNING
This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Indications: When the combination represents the dosage determined by titration: Adjunctive therapy in edema associated with congestive heart failure, hepatic cirrhosis, the nephrotic syndrome. Corticosteroid and estrogen-induced edema, idiopathic edema; hypertension, when the potassium sparing action of triamterene is warranted. Routine use of diuretics in healthy pregnant women is inappropriate; they are indicated in pregnancy only when edema is due to pathological causes (see Warnings).

Contraindications: Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available.

Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Watch for signs of impending coma in severe liver disease. If spironolactone is used concomitantly, determine serum K+ frequently; both can cause K+ retention and elevated serum K+. Two deaths have been reported with such concomitant therapy (in one, recommended dosage was exceeded, in the other serum electrolytes were not properly monitored). Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic anemia have been reported with thiazides. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effect may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances. Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and, rarely, allergic pneumonitis have occurred with thiazides alone.

Supplied: Bottles of 100 and 1000 capsules; Single Unit Packages of 100 (intended for institutional use only).

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Dermatology
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Lucius D. Hill, Seattle, Wa
Frank G. Moody, Salt Lake City, Ut

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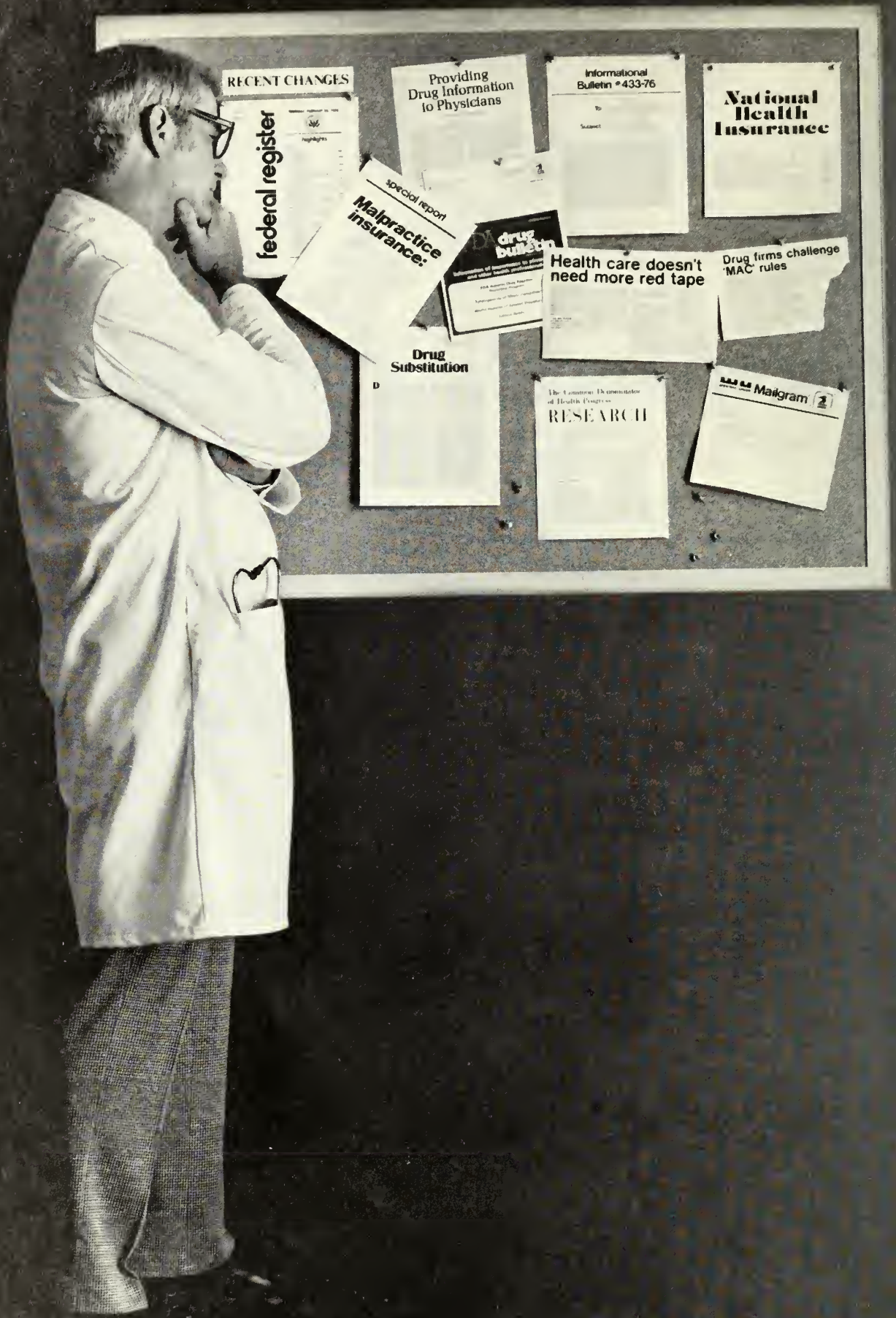
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THERE ARE A LOT OF PEOPLE GETTING BETWEEN YOU AND YOUR PATIENT.

Medicine today is in the spotlight, subjected to all kinds of scrutiny. Your control over patient therapy is being monitored, judged and occasionally abrogated, sometimes by unknown third parties.

The worry is that in the wake of this focus, the relationship between you and your patient will be weakened, without offsetting benefits. Consider three examples:

Drug substitution In most states, pharmacy laws, regulations or professional custom stipulate that your non-generic prescriptions be filled with the precise products you prescribe. But in the last five years, a dozen or more State laws have been changed, permitting the pharmacist in most cases to select a product of the same generic drug to fill any prescription.

Ironically, this dilution of physician control has taken place against a background of growing evidence that purportedly equivalent drug products may be inequivalent, since neither present drug standards nor their enforcement are optimal. In fact, the FDA itself says it has not enforced the same standards for hundreds of "follow-on" products that it had applied to the original NDA approvals. Thus physician control over patient therapy is being eroded with a risk that patients may be exposed to drugs of uncertain quality.

The major advertised claim for substitution is reduced prescription prices for consumers. Yet no documentation of any significant savings has been produced.

MAC Maximum Allowable Cost, MAC for short, is a Federal regulation designed to cut the Government's drug bill by setting price ceilings for drugs dispensed to Medicare and Medicaid patients. Unless the prescriber certifies on the prescription that a particular product is medically necessary, the Government intends to pay only for the cost of the lowest-priced, purportedly-equivalent, generally-available product. The effect of the program may be that elderly and indigent patients will be restricted to products which someone in Washington believes are priced right. Practicing doctors will have little to say about administration of the program, since Government will have absolute authority to make its choices stick.

The drug lag The future of drug and device research depends upon a scientific and regulatory environment that encourages therapeutic innovations. The American pharmaceutical industry annually is spending more than $1 billion of its own funds and evaluating more than 1,200 investigational compounds in clinical research. Disease targets include cancer, atherosclerosis, viruses and central nervous system disorders, among others. But there is a major barrier to the flow of new drugs to your patients: The cost of the research is more than ten times what it was, per product, in 1962; and whereas governmental clearance of new drug applications took six months then, it commonly consumes two years now.

The FDA needs adequate time, of course, to consider data. But it is equally clear that the present approval process contributes to needless delay of needed therapy. That's why the increased efficiency of the drug approval process is vital to all our futures.

If these issues concern you, we suggest that you make your voice heard—among your colleagues and your representatives in State legislatures and in Washington.

It could make a difference in your practice tomorrow.

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BOOKS RECEIVED

Books received by THE WESTERN JOURNAL OF MEDICINE *are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.*

ARTHRITIS SURGERY—Leonard Marmor, MD, Attending Surgeon, St. John's Hospital, Santa Monica, California; Lecturer, Prosthetics Education Project, University of California, Los Angeles, Center for the Health Sciences, Lea & Febiger, Washington Square, Philadelphia (19106), 1976. 548 pages, $48.50.

BASIC PSYCHIATRY—Third Edition—Myre Sim, MD(Edin), FRCP(Edin), FRC Psych, FRCP(C), DPM, Professor of Psychiatry, Faculty of Medicine, University of Ottawa, Ontario, Canada; and E. B. Gordon, MB, ChB(Edin), MRCPsych, DPM, Consultant Psychiatrist, Saxondale Hospital and General Hospital, Nottingham; Postgraduate Clinical Tutor, University of Sheffield; Clinical Teacher to the University of Nottingham. Longman, Inc., Churchill Livingstone—Medical Division, 19 West 44th St., New York City (10036), 1976. 306 pages, $11.00 (Softbound).

COMBINED TEXTBOOK OF OSTETRICS AND GYNAECOLOGY—Ninth Edition—Edited by James Walker, CBE, BSc, MD, FRCPG, FRCOG, Professor of Obstetrics and Gynaecology, University of Dundee: Honorary Consultant, Tayside Health Board; Ian MacGillivray, MD, FRCPG, FRCOG, Regius Professor of Obstetrics and Gynaecology, University of Aberdeen; Honorary Consultant, Grampian Health Board; Malcolm C. Macnaughton, MD, FRCPG, FRCOG, Muirhead Professor of Obstetrics and Gynaecology, University of Glasgow; Honorary Consultant, Greater Glasgow Health Board. Longman, Inc., Churchill Livingstone—Medical Division, 19 West 44th St., New York City (10036), 1976. 877 pages, $75.00.

ENDOSCOPY—Edited by George Berci, MD, Director, Department of Endoscopy, Cedars-Sinai Medical Center, Los Angeles; Attending Surgeon, Veterans Administration Hospital, Wadsworth; Clinical Associate Professor, Department of Surgery, University of California, Los Angeles, School of Medicine; with 58 coauthors. Appleton-Century-Crofts, A Publishing Division of Prentice-Hall, Inc., 292 Madison Avenue, New York City (10017), 1976. 805 pages, $78.50.

FLUORESCENT PROTEIN TRACING—Fourth Edition—R. C. Nairn, MD, PhD(L'pool), FRCPath, FRCPA, FRACP, FRSE, Professor and Chairman, Department of Pathology and Immunology, Monash University; Honorary Consultant Pathologist, Alfred Hospital, Prince Henry's Hospital and Queen Victoria Memorial Hospital, Melbourne, Australia; Foreword by J. R. Marrack, DSO, MC, MA, MD(Cantab), Emeritus Professor of Chemical Pathology, University of London. Longman, Inc., Churchill Livingstone—Medical Division, 19 West 44th St., New York City (10036), 1976. 648 pages, $45.00.

IMPLEMENTING THE PROBLEM-ORIENTED MEDICAL RECORD—Edition Second—Major Contributor: Lawrence L. Weed, MD; Editors: Jay S. Wakefield and Stephen R. Yarnall, MD. Medical Computer Services Association, 315 U-District Building, 1107 NE 45th St., Seattle (98105), 1976. 130 pages, $10.00 (Paperback).

LEGAL ASPECTS OF MEDICAL PRACTICE—Second Edition—Bernard Knight, MD(Wales), MRC Path, DMJ of Gray's Inn, Barrister-at-Law, Reader in Forensic Pathology, Welsh National School of Medicine, University of Wales, Cardiff; Honorary Consultant Pathologist, South Glamorgan Area Health Authority. Longman, Inc., Churchill Livingstone—Medical Division 19 West 44th St., New York City (10036), 1976. 254 pages, $14.50 (Softbound).

TRENDS IN HAEMATOLOGY—J. B. Chatterjea Memorial Volume—Editor: N.N. Sen, MD, DCP, MRC Path, FAMS, Professor, Division of Haematology, Department of Pathology & Bacteriology, Institute of Postgraduate Medical Education & Research, Calcutta; Associate Editor: A. K. Basu, MB, BS, PhD, MRC Path, MAMS, Reader, Department of Haematology, Calcutta School of Tropical Medicine, Calcutta. K. P. Bagchi & Company, 286 B.B. Ganguli Street, Calcutta (700012), India, 1975. 506 pages, $60.00.

(Continued on Page 10)

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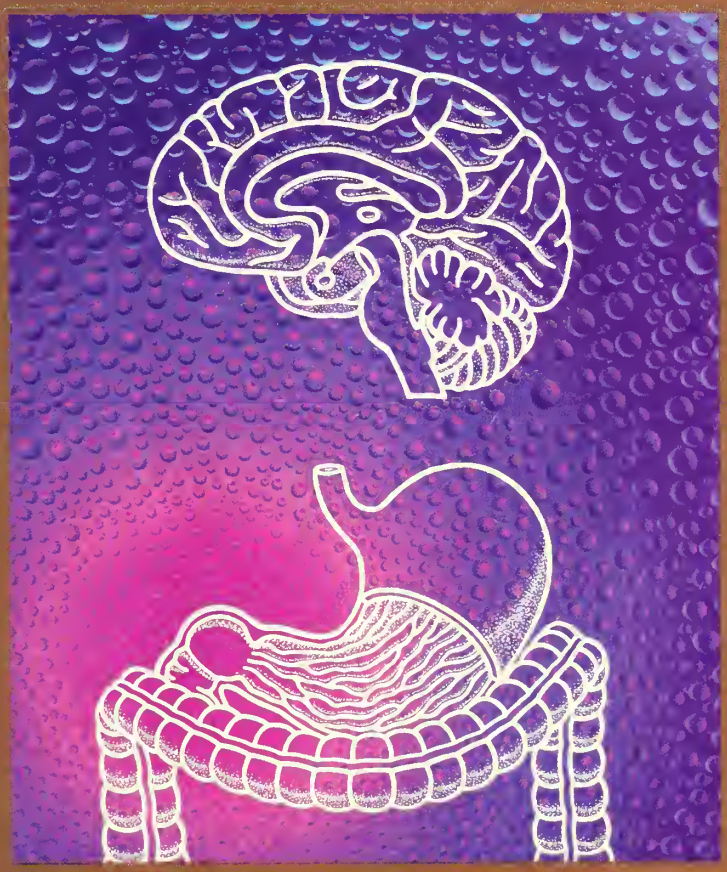

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PETTICOAT MEDIC IN VIETNAM—Adventures of a Woman Doctor—Diane L. Trembly, MD. Vantage Press, Inc., 516 West 34th St., New York City (10001), 1976. 275 pages, $6.95.

USES OF EPIDEMIOLOGY—Third Edition—J. N. Morris, CBE, MD(Hon), DSc, FRCP, Professor of Community Health, and Hon. Director, Medical Research Council's Social Medicine Unit, London School of Hygiene and Tropical Medicine, University of London. Longman Inc., Churchill Livingstone—Medical Division, 19 West 44th St., New York City (10036), 1975. 318 pages, $14.50.

AIDS TO POSTGRADUATE SURGERY—Meirion Thomas, MB, BS, MRCP, FRCS, Registrar in General Surgery, St. James' Hospital, Balham, London; and John S. Belstead, MB, ChB, FRCS(Edin), Registrar in Orthopaedic Surgery, Westminster Hospital, London. Churchill Livingstone - Medical Division, Longman Inc., 19 West 44th St., New York City (10036), 1976. 140 pages, $5.50 (paperback).

ALCOHOLISM AND THE BRAIN—A. E. Bennett, MD, The A. E. Bennett Neuropsychiatric Foundation, Berkeley. Stratton Intercontinental Medical Book Corporation, 381 Park Avenue South, New York City (10016), 1977. 86 pages, $9.75.

ANAESTHETICS FOR MEDICAL STUDENTS—8th Edition—Gordon Ostlere, MA, MB, B Chir (Camb), DA, FFARCS, Formerly Deputy First Assistant, Nuffield Department of Anaesthetics, University of Oxford; and Roger Bryce-Smith, MA, DM(Oxon), DA, FFARCS, Consultant Anaesthetist, University of Oxford; Formerly Assistant Professor of Anaesthesia, Western Reserve University, Cleveland. Churchill Livingstone - Medical Division, Longman, Inc., 19 West 44th St., New York City (10036), 1976. 140 pages, $6.00.

BACTERIOLOGY ILLUSTRATED—Fourth Edition—R. R. Gillies, MD, FRCPE, DPH, MRCPath, Professor of Clinical Bacteriology, The Queen's University of Belfast; Formerly Reader in Bacteriology, University of Edinburgh; and T.C. Dodds, FIMLT, FIIP, FRPS, Late Director of the Medical Photography Unit, University of Edinburgh. Churchill Livingstone - Medical Division, Longman, Inc., 19 West 44th St., New York City (10036), 1976. 247 pages, with colored illustrations, $26.00, cloth; $16.00, paper.

BLOOD GASES IN CLINICAL PRACTICE—Leopoldo Lapuerta, MD, Chairman, Department of Medicine, Medical Director of Respiratory Therapy, Santa Rosa Medical Center, Clinical Assistant Professor, Department of Medicine, University of Texas Medical School, San Antonio. Charles C Thomas, Publisher, 301-327 East Lawrence Avenue, Springfield, IL (62717), 1976. 117 pages, $12.50.

BRONCHO-PULMONARY IMMUNOPATHOLOGY—Claude Molina, Professor of Pneumo-phthisiology, University of Clermont-Ferrand, Clermont-Ferrand; Translated by J. Pepys, MD. FRCP, FRC Path, Professor of Clinical Immunology, Cardiothoracic Institute, University of London, Brompton Hospital. Churchill Livingstone - Medical Division, Longman, Inc., 19 West 44th Street, New York City (10036), 1976. 251 pages, $29.50.

CALCIUM PHOSPHATE AND MAGNESIUM METABOLISM—Clinical Physiology and Diagnostic Procedures—Edited by B.E.C. Nordin, MD, FRCP, DSc, Director and Professor of Mineral Metabolism, University of Leeds; Honorary Consultant Physician to the General Infirmary, Leeds. Churchill Livingstone - Medical Division, Longman, Inc., 19 West 44th St., New York City (10036), 1976. 683 pages, $60.00.

CEREBRAL ARTERIAL DISEASE—Edited by R.W. Ross Russell, Physician to the Department of Neurology, St. Thomas' Hospital; The National Hospital for Nervous Diseases, Queen Square, and Moorfields Eye Hospital, City Road, London. Churchill Livingstone - Medical Division, Longman Inc., 19 West 44th St., New York City (10036), 1976. 323 pages, $30.00

CLINICAL GASTROENTEROLOGY—Second Edition—Howard M. Spiro, MD, Professor of Medicine, Yale University School of Medicine; Attending Physician (Director, Gastroenterology Section), Yale-New Haven Hospital, Consultant in Gastroenterology, Hospital of St. Raphael, New Haven; VA Hospital, West Haven; Griffin Hospital, Derby; Waterbury Hospital, Waterbury; Park City Hospital, Bridgeport; William W. Backus Hospital, Norwich, Connecticut; The Cape Cod Hospital, Hyannis, Massachusetts. Macmillan Publishing Co., Inc., 856 Third Avenue, New York City (10022), 1977. 1289 pages, $45.00.

CLINICAL ORTHOPAEDIC EXAMINATION—Ronald McRae, FRCS, Consultant Orthopaedic Surgeon, Southern General Hospital, Glasgow; Honorary Clinical Lecturer in Orthopaedics, University of Glasgow; Lecturer in Surgery and Orthopaedics, Glasgow School of Occupational Therapy; Lecturer in Anatomy, Glasgow School of Chiropody; Fellow of the British Orthopaedic Association and Member of the Institute of Medical and Biological Illustration. Churchill Livingstone - Medical Division, Longman Inc., 19 West 44th St., New York City (10036), 1976. 219 pages, with original drawings by the author, $11.50 (softbound).

CURRENT MEDICAL DIAGNOSIS & TREATMENT 1977—16th Edition—Marcus A. Krupp, MD, Clinical Professor of Medicine, Stanford University School of Medicine; Director of Research, Palo Alto Medical Research Foundation; Director of Laboratories, Palo Alto Medical Clinic; Milton J. Chatton, MD, Clinical Professor of Medicine, Stanford University School of Medicine; Senior Attending Physician, Santa Clara Valley Medical Center, San Jose; Research Associate, Palo Alto Medical Research Foundation; and Associate Autho:s. Lange Medical Publications, Drawer L, Los Altos, CA (94022), 1977. 1066 pages, $16.00.

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Treponema pallidum—As an alternate treatment in patients allergic to penicillin.

C. diphtheriae and C. minutissimum—As an adjunct to antitoxin. In the treatment of erythrasma.

Entamoeba histolytica—In the treatment of intestinal amebiasis.

L. monocytogenes—Infections due to this organism.

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Contraindications:

Known hypersensitivity to erythromycin.

Warnings:

Safety for use in pregnancy has not been established.

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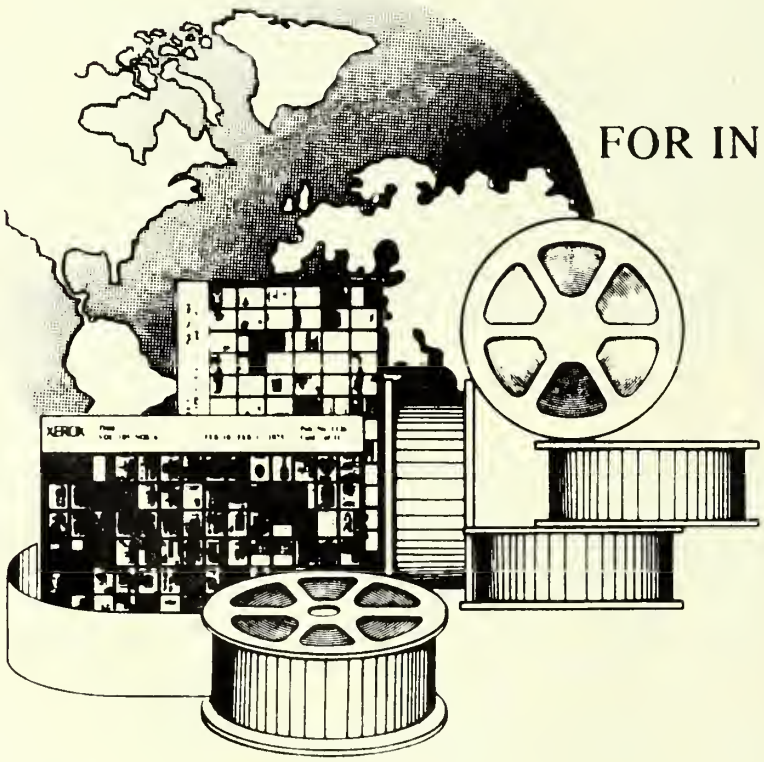

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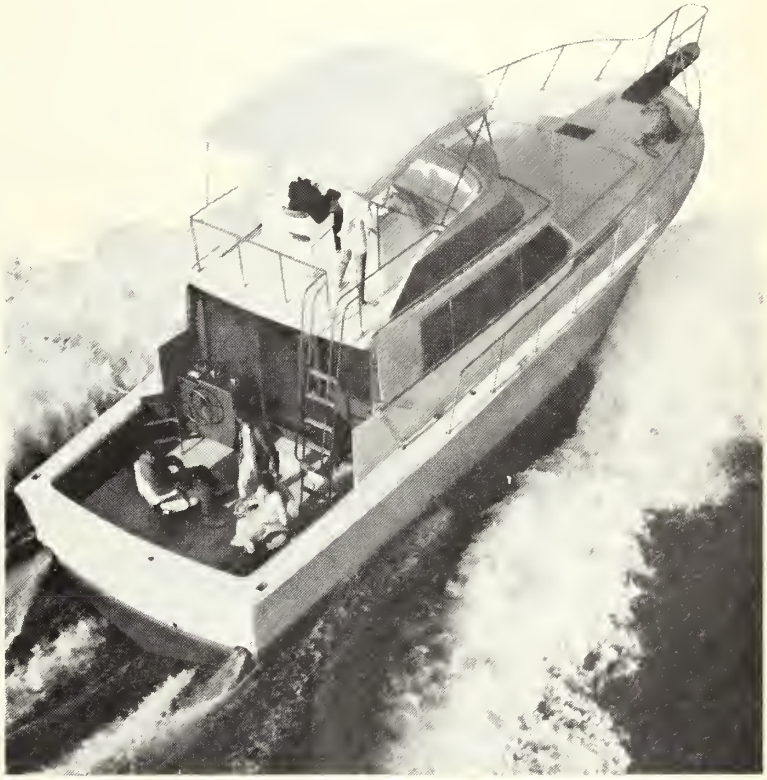

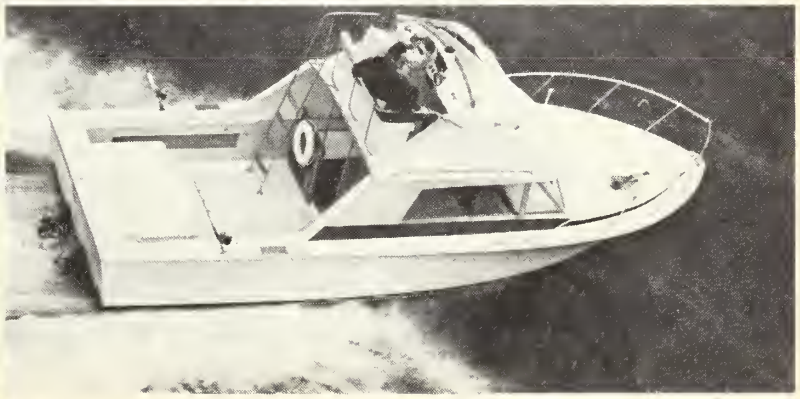

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Refer to: Dean TM: Carcinoma of the colon and rectum—A perspective for practicing physicians, with recommendations for screening. West J Med 126:431-440, Jun 1977

Carcinoma of the Colon and Rectum

A Perspective for Practicing Physicians, with Recommendations for Screening

THOMAS M. DEAN, MD, *Hyden, Kentucky*

Carcinoma of the colon and rectum is the most common serious type of cancer found in the United States and is second only to lung cancer among causes of death from cancer. Its cause is unknown but several environmental factors—especially low bulk, high fat diets—seem to predispose to its development. The disease is readily treatable by surgical operation if it is diagnosed early. Radiation and chemotherapy may offer some additional benefit in treating advanced disease but the response to all forms of therapy is disappointing in patients in whom disease has spread beyond the bowel wall. Colorectal cancer appears to be a very slowly progressive disease with a long asymptomatic period providing an ideal opportunity for diagnosis at an early treatable stage. Both proctosigmoidoscopy and screening specimens of stool for occult blood have been shown to be effective methods for identifying it before symptoms develop. These procedures should be done routinely in all patients over 40 years old and especially in those patients who have other risk factors such as positive family histories or hereditary conditions known to predispose to colorectal cancer.

IN SPITE OF THE FACT that it has received somewhat less attention than other major types of cancer, namely lung and breast cancer, carcinoma of the colon and rectum is the most commonly diagnosed serious variety of cancer[1] in the United States (second only to skin cancer in number of new diagnoses per year). Among causes of death from cancer it ranks second only to lung cancer (Table 1).

Unlike some kinds of cancer, such as that of the stomach and the uterus in which the mortality appears to be leveling off or actually decreasing, all indications are that in the future colorectal carcinoma will be an increasingly important cause of mortality and morbidity.

In approaching a problem of this magnitude both from a purely medical and from a public health point of view, a number of questions need to be answered:

- Can the disease be prevented?
- Do effective therapeutic modalities exist for dealing with the disease after it develops?
- Does the efficacy of therapy depend on the stage or extent of spread of the disease? That is, does earlier diagnosis make a difference?
- Do techniques exist for detection of the disease before it becomes clinically evident?
- Are the available diagnostic techniques acceptable in terms of reliability, risk, patient com-

From the Department of Family Medicine, University of Washington School of Medicine, Seattle. Dr. Dean is now with the Frontier Nursing Service, Hyden, Kentucky.

Submitted, revised, October 4, 1976.

Reprint requests to: Thomas M. Dean, MD, Frontier Nursing Service, Hyden, KY 41749.

TABLE 1.—*Number of Diagnoses and Deaths for Five Leading Cancer Sites*[1]

	Estimated New Cases 1974	*Estimated Deaths 1974*	*Deaths 1969*
Colon and Rectum	99,000	48,000	45,274
Lung	83,000	75,400	61,843
Female Breast	89,000	32,500	28,830
Uterus	46,000*	11,200	12,475
Prostate	54,000	18,000	16,836

*Does not include carcinoma *in situ* of cervix.

pliance and cost so that they can be applied to large numbers of asymptomatic patients?

- How often and to what patient groups should these diagnostic tests be applied?

Unfortunately, the available information is not adequate to completely answer all of these questions. Nonetheless, a large body of data and experience does exist. This paper attempts to summarize it and make some recommendations about the approach that the practicing physician should take toward this problem.

Can the Disease Be Prevented?

Answering this question depends to a large extent on understanding the cause of the disease and this remains largely in the realm of speculation. However, a number of very interesting associations have been identified and several intriguing hypotheses have been generated.

Most current theories implicate environmental factors, primarily dietary, in the causation of large bowel cancer. These theories are based on epidemiological observations which have shown that the incidence of colorectal cancer is low in underdeveloped areas in Africa and Asia. The rates increase in countries where Western influence is greater with the highest rates being found in Britain and the United States. In countries that have relatively recently taken on a more Western life style, such as Japan and Italy, mortality rates from large bowel cancer are rising toward those of the United States and Britain.[2] The fact that environmental influences are more important than genetic characteristics has been shown in immigrant populations, particularly among Japanese immigrants to Hawaii and California.[3] With the change in environment the rates of colorectal cancer begin to increase and approach those of the host population. A similar trend is found among blacks in the United States.[2]

British epidemiologist Denis Burkitt was one of the first to attempt to dissect these differences and he has shown that similar variations are true for other noninfective diseases such as coronary heart disease, gallstones, appendicitis, varicose veins and diverticulosis as well as benign and malignant tumors of the large bowel.[4,5] He has shown that the fiber content of the diet in these populations differs greatly and that an increased amount of dietary fiber correlates both with an increase in the volume of stool produced and with the rate at which it traverses the intestine.[6] On the basis of these data Burkitt has hypothesized that decreased stool volumes and increased transit times have enhanced the effect of potential carcinogens in the feces by prolonging their contact with the intestinal mucosa. He feels the data are conclusive enough to begin a campaign to change Western dietary habits away from refined carbohydrates toward foods with higher fiber content.[4,5]

Other investigators have implicated the protein and fat components of the diet and have questioned Burkitt's conclusions about fiber. Drasar[7] found no correlation between total fiber content of the diet and colon cancer. Hill and others[8,9] have shown that with an increase in the fat content of the diet there is an increase in the concentration of bile steroids in the feces and an increase in the ratio of anaerobic to aerobic bacteria in the intestinal flora. Anaerobic bacteria metabolize bile steroids more actively than do aerobes and produce compounds such as deoxycholic acid which are thought to be carcinogenic. Hill and colleagues showed that not only were the substrates for these reactions present in higher concentrations in feces from people consuming a Western diet, but also the intestinal flora from these groups had a greater capacity to transform them into compounds thought to be carcinogenic. They have also shown[9] that within a culturally homogeneous group, patients with colon cancer had higher levels of fecal bile acids and greater amounts of anaerobic bacteria than did control patients. As an aside, they reported some evidence to indicate that the use of cholestyramine to lower serum cholesterol levels may increase fecal bile acids and predispose to colon cancer.

Wynder[10,11] has corroborated the findings of Hill's group and in addition showed that a change in diet can relatively rapidly bring about changes in both the chemical and bacterial makeup of the stool. Volunteers who had been consuming "a mixed Western, high meat, high fat diet" were switched to a meat free diet. After four weeks

the investigators were able to show that the subjects had significantly fewer anaerobic bacteria in their feces as well as lower levels of a number of neutral sterols and bile acids.

Whether the major etiological factor is a decrease in dietary fiber or an increase in fat and protein (or both, since the two changes often parallel each other) is still a subject of vigorous debate. However, the data implicating dietary factors are compelling.[12] While there is, as yet, no proof that dietary intervention will be effective in protecting against the disease, this issue demands further exploration. Even in the absence of such proof, attempts at dietary intervention may be justified.

Therapeutic Modalities

As with other forms of cancer, surgical operation, radiation and chemotherapy have all been used, but surgical excision remains the basic form of therapy and the only one which offers a chance of cure. However, as shown below, its effectiveness is highly dependent on the extent of the disease at the time of operation.

The exact roles of radiation and chemotherapy are not well defined. Both have been shown to provide some therapeutic benefits, especially in patients with advanced disease.[13-16] However, the magnitude of these contributions has been small and at present it does not appear that these modalities can make any major change in the overall morbidity and mortality from carcinoma of the colon.

There is no question that effective therapy does exist. However, the benefits are limited to certain groups of patients and as shown below the overall mortality from colorectal carcinoma remains high.

The Effect of the Disease's Stage

There is no doubt that the efficacy of treatment depends on the stage of the disease. As a number of large studies (Table 2) have shown, localized disease that can be completely resected carries a good prognosis, and survival rates diminish as the extent of the disease increases. It should be noted that when the data are age adjusted the survival rates for stage A patients is very close to that of the general population. Also, Lanier[21] has shown that ten-year survival rates are almost identical to five-year survival rates, indicating that patients who are alive at five years may be considered cured. MacLeod[22] and Gilbertsen[24] have indicated that for patients with localized disease those who survive two to three years may be considered cured.

The prognostic importance of the stage of the disease is supported by data comparing the survival rates of patients in whom symptoms are present with those in patients without symptoms. Scudamore[25] reported a five-year survival rate of 88 percent in patients who had no symptoms

TABLE 2.—*Survival Rates by Stage at Diagnosis*

Author	*Source*	*Number of Patients*	*Percent Five-Year Survival—Dukes Classification*				
			A	*B*	*C*	*D*	*Overall*
Corman[17]	Lahey Clinic, Boston	513	84	65	36	0	..
			98*	79*	42*	..	..
Hight[18]	Memorial Hospital, Worcester, Massachusetts	216	68	53	44	0	44
Falterman[19]	Charity Hospital, New Orleans	1,808	58	40	16	5	24
Weir[20]	Population of Southern Saskatchewan	642	74	60	36	0	35
Lanier[21]	Population of Rochester, Minnesota	439	88*	B1 92* B2 68*	27*	..	61*
			89†	99† 66†	19†	..	60†
MacLeod[22]	Victoria General Hospital Halifax, Nova Scotia	375	85*	65*	C1 35* C2 5*	..	33*
Sanfelippo[23]	Mayo Clinic, Rochester, Minnesota	391	A&B 63		C&D 31		52
Gilbertsen[24]	University of Minnesota	1,852	59		..	..	31

Dukes Classification
Stage A—Lesion confined to mucosa
B—Direct invasion to serosal fat without lymph node involvement.
B1—confined to bowel wall with negative nodes
B2—through bowel wall with negative nodes
C—Positive lymph nodes involvement
C1—only local nodes positive
C2—central nodes positive
D—Distant metastases

*Age adjusted survival rates.
†10-year age adjusted survival rates.

at the time of diagnosis as compared with 25 percent for those with symptoms. Sanfelippo[23] showed a difference of 71 versus 49 percent. The most common symptoms in several series[17,19,26,27] were abdominal pain or distention, change in bowel habits, gross rectal bleeding and weight loss. Palpable mass and anemia were commonly found on initial evaluation. There appears to be little difference in the diagnostic significance of any individual symptom except that the existence of any of them notably worsens the prognosis.

The conclusion of virtually every author commenting on the subject has been that therapeutic efforts can be truly effective only in early localized disease and that to improve the outlook significantly for patients with colorectal carcinoma we must achieve earlier diagnosis.

Detecting the Disease Before It Becomes Clinically Evident

From the previous discussion it is evident that we cannot rely on the appearance of symptoms if we are to diagnose the disease at a treatable stage. There are essentially five techniques which have been promoted for presymptomatic diagnosis: digital rectal examination, proctosigmoidoscopy, detection of fecal occult blood, detection of carcinoembryonic antigen (CEA) and barium enema.

Barium Enema Studies

While a barium enema study is an unquestionably reliable technique it has little usefulness as a primary diagnostic tool because of its expense, inconvenience and discomfort, as well as the radiation exposure involved. It will undoubtedly retain its usefulness as a second level diagnostic test but we must look elsewhere to find test for population screening. Similar comments apply to colonoscopy.

Carcinoembryonic Antigen Tests

In 1965 Gold and co-workers reported the discovery of a glycoprotein which they called carcinoembryonic antigen (CEA). It appeared to be present in malignant disease of the gastrointestinal tract but absent in normal colic tissue and in the serum of patients with benign disease of the gastrointestinal tract. This discovery raised the possibility of using a relatively simple serological test for screening for asymptomatic gastrointestinal cancer, particularly colorectal cancer. Findings in subsequent studies, however, have shown that CEA is a relatively insensitive indicator of early localized colorectal cancer (40 percent positive) and tests for it are consistently positive only in patients with widespread disease and distant metastases (85 to 95 percent positive).[28-30] Furthermore, it has been shown that tests for CEA are positive in patients with nonmalignant conditions such as chronic lung disease and ulcerative colitis. Because of this the procedure appears to have little usefulness in early diagnosis of colorectal cancer. It may, however, have value in determining the adequacy of resection: it has been shown that in patients in whom there have been positive CEA results, there is a change to negative if tumors are completely resected. In addition, a rise in CEA titer after resection may be the earliest indication of recurrent tumor.[29,31]

Proctosigmoidoscopy

Direct visualization of the distal portion of the large bowel by use of a sigmoidoscope has long been an accepted approach to diagnosis of path-

TABLE 3.—*Results of Screening for Colorectal Cancer with Sigmoidoscopy*

Author	*Population*	*Number of Patients*	*Number with Cancer*	*Cases of Cancer per 1000 Examinations*	*Significant Findings Other than Cancer (Percent of Patients)*
Portes (1957)[33]	Asymptomatic patients at Cancer Detection Center	50,000	347	6.9	7.3
Hertz (1960)[34]	Asymptomatic patients at Strang Clinic-Sloan Kettering Institute	26,126	58	2.2	..
Mortel (1966)[35]	Asymptomatic patients at Mayo Clinic	1,020	0	0	10
Rasgon (1969)[36]	Asymptomatic patients at Strang Clinic	1,900	8	4.2	6.2
Weiss (1972)[37]	Asymptomatic patients admitted to psychiatric ward	1,000	4	4.0	..
Gilbertson[38]	Asymptomatic patients in University of Minnesota Cancer Detection Center	12,000	19	1.6	..
Powers[39]	Asymptomatic patients in a group of private practices	694	2	2.9	11.3

ology in that region and has been advocated as the best screening technique for colorectal cancer. Roughly two thirds of all malignant disease occurs in the rectum and sigmoid[32] though the amount accessible to the sigmoidoscope is somewhat less than that because not all of the sigmoid is within reach of the standard 25 cm instrument. Nonetheless, as shown in Table 3, a number of large studies have shown that this is a useful technique in the diagnosis of colorectal cancer in asymptomatic patients.

Recent data about the value of proctosigmoidoscopy with polypectomy have come from the University of Minnesota Cancer Detection Center where over the past 25 years 18,158 asymptomatic patients have been observed and 103,645 sigmoidoscopies carried out, 85,487 of which were annual follow-up examinations.[40] On the basis of epidemiologic and demographic data they anticipated they would find 75 to 80 cases of carcinomas in the course of the follow-up examinations but instead they found only 11, all of which were early localized tumors without spread beyond the bowel wall. The patients in the cases discovered during follow-up examinations had a five-year survival rate of 80 percent as opposed to 40 percent as a national average. These data suggest that routine screening proctosigmoidoscopy with polypectomy can identify colorectal cancer at an earlier stage than would otherwise have been accomplished. The data support the hypotheses of others[41,42] that many polyps are premalignant lesions and that their removal will reduce the subsequent incidence of disease.

Testing for Occult Gastrointestinal Bleeding

Testing stool specimens for occult blood is a technique that has long been mentioned as a screening tool for colorectal neoplasms. The various available chemical tests have a number of characteristics that make them attractive as screening tools: they are cheap, require little professional time or equipment to administer or process, and can be done with little in the way of patient inconvenience or discomfort. The difficulties relate to two general areas: (1) confusion about the reliability of the various tests and about the significance of positive reactions and (2) lack of data about how often colorectal cancer exists without producing occult bleeding (the incidence of false negative results).

With regard to the question of interpretation of positive results, most of the confusion is due to the wide range of sensitivity testing procedures available. Chemical tests for occult blood have used one of three basic reagents—guaiac, benzidine or orthotolidine. These tests depend on the production of a blue dye from oxidation of phenolic compounds. Numerous compounds are capable of catalyzing this reaction including naturally occurring peroxidases and hemoglobin which exerts a peroxidase-like activity.

Recently Ostrow[43] and Morris[44] have carefully evaluated the reliability of conventional liquid guaiac solutions (saturated and diluted), a guaiac slide test (Hemoccult™) and an orthotolidine tablet test (Hematest™) using normal volunteers who ingested chromium (Cr)-labeled red cells. They found as previous studies had shown that both liquid guaiac reagents and the Hematest tablets had an unacceptable incidence of false positive reactions (49 percent, 42 percent and 27 percent, respectively) for subjects on an unrestricted diet. In the same population the Hemoccult slide test had only 1 percent false positives. When volunteers were placed on a diet containing no red meat, soya products or horseradish and subsequently given labeled red cells via nasogastric tube it was found that the former two tests still had a high incidence of false positives though somewhat lower than before (see Table 4). In terms of sensitivity the Hemoccult slide test was significantly less sensitive than the other two.

With regard to the effect of diet on the tests, these authors found that the incidence of false positive results with the guaiac solution and the Hematest were significantly decreased when meat products were eliminated while the results on the Hemoccult slides were essentially unaffected by diet. Storage of the stool specimens had little effect on the reading of the Hemoccult slides. Comparisons of results of independent testing by two different observers showed that the reproductibility of Hemoccult was superior to all other methods tested.

They concluded that even though Hemoccult is significantly less sensitive than other methods tested it is "sufficiently sensitive to detect most occultly bleeding lesions."[44] This, together with its low incidence of false positive reactions and ease of administration make it, in their opinion, the method of choice for screening stool specimens for occult blood.

A similar though somewhat different perspective has been offered by Greegor who has written

extensively about the use of Hemoccult slides in screening for colorectal cancer.[26,45,46] He had become disenchanted with the return from routine sigmoidoscopy and in reviewing cases of patients in his practice with colon cancer he found that in seven of eight, stool specimens had been guaiac positive. Subsequently he began screening patients using Hemoccult slides and obtaining two specimens from each of three separate bowel movements. In 29 of 128 asymptomatic patients (23 percent) there was at least one positive test but in only two of these was cancer found. In an attempt to make the examination more discriminating he put patients on a meat free, high bulk diet which emphasized vegetables and bran with the rationale that this would reduce false positives and that the abrasive action of the fiber would increase the incidence of detectable bleeding from asymptomatic lesions.[45,46] Using this technique in a series of 278 asymptomatic patients he found three unsuspected cases of cancer (10.8/1,000) and a total of 24 patients in whom at least one stool specimen was positive. In the latter group all but three were found to have some form of gastrointestinal pathology to explain the positive test results. He concluded that screening for occult bleeding with Hemoccult slides is the most effective procedure for detecting early colorectal cancer but felt that to be reliable it had to be used in conjunction with a meat free, high bulk diet.

Recent studies, then, are in general agreement that Hemoccult slides are the method of choice for screening of occult bleeding. The data indicated that while it is less sensitive than other methods the level of sensitivity is acceptable and that the level of specificity is superior to all other available tests. The necessity for dietary restriction has not been proven in any controlled fashion but this may increase the accuracy of the procedure.

Data about the incidence of occult blood loss in patients with asymptomatic lesions are difficult to find, but all indications are that blood loss occurs early in the course. Cole[47] has stated that in 80 percent of colorectal cancers there is occult blood loss but gives no data to substantiate this. Greegor[26] says that he is unaware of any true false negatives in ten years of screening with Hemoccult slides. De Peyster[48] reports that in 90 percent of patients either occult or gross blood is present in stool.

In a mass screening program for colorectal cancer using Hemoccult slides, Hastings[49] found five asymptomatic malignant lesions in a group of 2,272 adults over age 40 (2.2 cases of cancer per 1,000 patients), a pick-up rate similar to those in the various series of which sigmoidoscopy was the primary screening tool. In this series the actual pick-up rate was probably considerably higher than that reported because in only about a third of the patients was a complete workup done after occult bleeding was identified. These data support the thesis that most malignant lesions bleed early in their course and that detection of occult blood loss is at least as sensitive and probably more so than sigmoidoscopy in detecting asymptomatic lesions. Theoretically one would expect this to be the case since if the tumors bleed early the tests for occult blood loss

TABLE 4.—*Comparison of Tests for Fecal Occult Blood**

Stool Hemoglobin Concentration (mg/gm)	*Percent Positive Results*		
	Saturated Guaiac Solution	*Hematest (Orthotolidine)*	*Hemoccult*
GROUP I			
0	43 (37/87)	23 (20/89)	1 (1/88)
<5	59 (19/32)	43 (14/32)	6 (2/32)
5-10	100 (13/13)	69 (9/13)	54 (7/13)
10-15	100 (9/9)	89 (8/9)	78 (7/9)
>15	100 (8/8)	100 (9/9)	100 (7/7)
GROUP II			
0-2.0	80 (99/124)	80 (99/124)	11 (13/124)
2.1-10.0	87 (33/38)	84 (32/38)	50 (19/38)
10.1-50.0	100 (23/23)	96 (22/23)	78 (18/23)

GROUP I = Normal volunteers who ingested ^{51}Cr-labeled red cells.

GROUP II = Patients known to have occult gastrointestinal bleeding given ^{51}Cr-labeled red cells intravenously.

*Adapted from Ostrow[43] and Morris.[44] Results given in percentages with actual number in parentheses.

should identify lesions throughout the colon whereas sigmoidoscopy is useful only in the distal 25 cm.

Digital Rectal Examinations

The standard rectal examination has long been promoted as a screening procedure for colorectal carcinoma and as an initial step in the evaluation of lower gastrointestinal symptoms.

It is mentioned here primarily to caution against overdependence on it as a screening test. There is no question that it is a simple and direct procedure and therefore is attractive from the point of view of screening. Its weakness stems from the fact that only 10 to 12 percent of bowel cancer is palpable on digital examination. None the less, it is a valuable procedure because it provides information about a segment of the colon where other tests are less reliable and it usually provides a specimen of stool for occult blood testing.

Diagnostic Techniques in Asymptomatic Patients

Reliability

With regard to sigmoidoscopy the University of Minnesota experience[40] together with data from Hertz,[34] Rasgon[36] and others indicate that this technique can reliably identify early cancer in the rectum and distal colon. It obviously has no usefulness for lesions above the proximal sigmoid.

Testing for occult blood, on the other hand, can potentially pick up lesions throughout the colon but the precise incidence of false positives and false negatives is not well defined. As previously discussed, the incidence of true false negatives is low and should approach zero if patients have regular testing. With Hemoccult slides the incidence of true false positives (positive test without any identifiable source of blood loss) is probably in the range of 5 to 20 percent and may be reduced by dietary manipulation as discussed above. Acceptability has to be determined within the context of a given population, institution or practice, but these would seem to be within reasonable limits.

Risk

There is no risk to patients from testing for occult blood and the risk from sigmoidoscopy is low, the main risk being perforation. Perforation below the peritoneal reflection usually has no serious implications but perforation above that point necessitates abdominal exploration and repair. At the University of Minnesota[40] there have been five perforations in 103,000 examinations—none in the last 50,000—for an average of 1 per 20,600 examinations (0.02 percent). This is consistent with Bolt's[50] estimate of a morbidity rate of 0.002 percent to 0.07 percent. If the scope is passed without force and minimal air insufflation is used the risks are minimal and well within the acceptable range.

Patient Acceptance

To a large extent acceptance by patients depends on the way the program is presented and the vigor with which follow-up is pursued. Available studies show that sigmoidoscopy can be used routinely in large populations of patients. No one, however, would contend that it is a pleasant procedure and it is potentially painful, which makes regular repeat examinations less attractive. Routine testing for occult blood is painless and much preferable to sigmoidoscopy in this regard.

Cost

The cost of screening using Hemoccult slides is about 15 cents per slide for the materials and a small additional amount for processing. If four slides are used per patient and repeated yearly the cost should be $1 to $3 per patient per year.

The cost of sigmoidoscopy varies depending on how many of the studies are done and how well equipped the institution is to do them. Gilbertsen[40] estimates that the procedure should cost $11.73 while other estimates are between $30 and $50.[50,51] Is this an acceptable cost? Gilbertsen has calculated that the expense of routine sigmoidoscopy and of treating early lesions is equal to the current cost of treating more advanced disease which occurs when screening is not practiced. His argument is that if screening were routinely used there would be no additional expense but morbidity and mortality would be notably reduced. Various other estimates[50,51] have placed the cost of detecting a case of asymptomatic cancer at between $10,000 and $70,000. Again it is hard to define acceptability because one always has to consider the resources available within a given situation. The bulk of the data indicate that this is a worthwhile expenditure; however, if occult blood testing proves to be as reliable it is both simpler and far cheaper.

Who Should Be Tested and How Often?

If the returns from screening are to be maximized then it must be directed to those groups at greater risk for development of the disease. The time intervals between tests must be consistent both with the natural history of the disease and with the realities of cost and patient compliance.

In identifying high risk groups, age is the primary risk factor with 90 percent of intestinal cancer deaths occurring in patients over the age of 52.[40] As shown in Table 5, colorectal cancer is very rare under the age of 40. Above that age the numbers increase, with most deaths occurring in the seventh and eighth decades.

In addition to age several other risk factors have been identified. These have been summarized by Schottenfeld[52] as shown in Table 6.

The natural history of colorectal cancer has not been precisely defined but all indications are that it is a very slowly growing tumor with a long asymptomatic period. Initially it spreads by local invasion and distant metastasis usually occurs only much later in its course.

The best data regarding the rate of growth come from Welin's study[53] of 375 tumors that were not resected but rather followed by repeat barium enema. He found that the time required for doubling of the size of the tumors ranged from 138 to 1,155 days within a mean doubling time of 620 days. Spratt[54] followed one tumor for 7.5 years and found a doubling time of 636 days. Both Welin and Spratt found that the growth rate of metastatic lesions in a closed space was five to six times as fast as the primary. They attributed this to the abrasive action of feces on the intraluminal portion of tumor producing sloughing of surface layers. Hertz[34] described two cases of colorectal cancer that were diagnosed by biopsy but were not operated on until 4 and 13 years later at which time both were still stage A lesions. On the basis of a variety of pathological studies, Morson[42] feels that it takes at least five years for cancer to evolve in a polyp and on the average much longer than that.

TABLE 6.—*Risk Factors in Colon and Rectum Cancer**

Factor	*Approximate Relative Risk (relative risk for general population equal 1.0)*
Family history of large intestinal cancer	3.0
Previous primary female genital cancer	2.0
Previous colon or rectum cancer	3.0
Previous colon or rectum cancer in association with adenomatous polyps in resected specimen	6.0
Chronic ulcerative colitis	10.0
Familial polyposis coli	10.0-25.0

*Adapted from Schottenfeld.[52]

These data indicate that colorectal cancer is a very slowly progressive disease with a long asymptomatic interval. This means that the period during which it can be effectively treated is relatively long, which in turn provides an ideal opportunity for screening.

The appropriate interval between screening tests depends on the natural history of the disease, the expense and difficulty of the test and the test's sensitivity. With regard to fecal occult blood testing, the procedure is simple, inexpensive, and probably quite sensitive. In that situation annual screening would seem to be adequate and if the test proves to be highly sensitive a longer interval between tests may be justified.

With respect to sigmoidoscopy the procedure is more difficult and expensive but has a high sensitivity. In view of the relatively low pick-up rate on follow-up examinations, Gilbertsen[40] has suggested that sigmoidoscopy every two to three years should be adequate to detect malignant lesions before their spread. Drexler[55] feels that intervals up to six years are appropriate for younger patients and those with no polyps.

The participants at the Colon Cancer Workshop at the National Conference on Cancer Pre-

TABLE 5.—*Distribution of Colorectal Cancer by Age*

Author	*Number of Patients*	<40	40-49	50-59	60-69	70-79	80+
Hight[18]	216	2	8	16	26	31	17
Weir[20]	616*	4	9	16	28	31	12
Lanier[21]	439	3	7	23	23	25	20
Berardi[27]	103	2	17	15	28	35	3
TOTALS	1,374	(3)	(9)	(18)	(26)	(29)	(15)

Figures in parentheses are average percentages in each age group.

*Colon cancer only.

vention and Detection[56] recommended that all asymptomatic patients over the age of 40 be screened for blood in the stool and that those with positive findings be followed up with proctoscopy, barium enema and upper gastrointestinal series. In addition, they recommend that all patients over the age of 40 should have proctosigmoidoscopy at least every three years.

Recommendations

- Unless there are specific contraindications, all patients should be advised to minimize the amount of animal fat in their diets and to increase the fiber content by emphasizing unrefined cereals, fresh vegetables and the like.
- All patients over the age of 40 should be screened annually for the presence of occult blood in stool. Four to six specimens from at least three different stools should be tested yearly using Hemoccult slides. The use of a high bulk, meat free diet prior to and during the testing period is not essential but may increase the accuracy of this method.
- All patients over the age of 40 should have proctosigmoidoscopy with removal of all polypoid lesions every three years and more frequently if there is any suggestion of rectal or colonic abnormality. If screening for fecal occult blood proves to be sufficiently reliable then proctosigmoidscopy may be necessary only as a second level test in those patients with occult bleeding.
- Those patients with specific risk factors in addition to age (such as a positive family history for colorectal or other major cancer, history of ulcerative colitis, familial polyposis or Gardner's syndrome) deserve special attention to insure that they receive regular evaluation. At this time, however, there is no evidence that the natural history of colorectal cancer is different in these patients than in the general population.

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The Effectiveness of Loop Diuretics in Treatment of Hypertension

How effective are the new loop diuretics—furosemide (Lasix®) and ethacrynic acid edecrin—in treatment of hypertension?

I don't think the loop diuretics have greatly enhanced our ability to deal with hypertension. They're more potent diuretics, but they don't have any advantage in the treatment of hypertension over the old thiazides, except for one situation—and that situation is in the patient who has chronic renal failure. When the glomerular filtration rates gets down below 30, which means the blood urea nitrogen level has started up in the range of 50 or 60 and the creatine is over 2, then the thiazides are no longer effective as diuretics whereas the loop diuretics, either furosemide or ethacrynic acid, are effective. So the only time that I use the loop diuretics in the treatment of hypertension is in a patient who has chronic renal failure along with hypertension, in which case the old thiazides will not be effective. You have to use more than the recommended doses if you're going to treat a patient with chronic renal failure with furosemide. Instead of 40 mg twice a day or three times a day as recommended on the package insert, it may have to be 240 mg three or four times a day. You have to titrate this; you don't dare start out with that big a dose, but sometimes it takes that much to get a natriuretic effect in a patient with chronic renal failure. Ethacrynic acid is not well tolerated; it has a lot of gastrointestinal side effects and I don't think it has much of a role. It's certainly just as potent as furosemide, but furosemide is better tolerated.

—RAY GIFFORD, MD, *Cleveland*

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Pneumocystis Carinii Pneumonia in Children

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From a retrospective study at the University of California, San Francisco, Medical Center, it is evident that pneumocystic carinii pneumonia is being seen more frequently as a secondary complication to the use of immunosuppressive drugs. This disease presents with nonspecific respiratory symptoms, therefore a high degree of suspicion and knowledge of the population at risk are necessary for an early diagnosis. Except for x-ray films of the chest, physical and laboratory studies are of minimal diagnostic value. In a patient with compromised immune defenses and respiratory distress, bilateral diffuse reticular infiltrates seen on a film of the chest are highly suggestive of pneumocystis carinii pneumonia. The diagnosis should be confirmed histologically because a variety of pathogens can cause these findings and each requires a specific treatment. At our institution, open thoracotomy is the method of choice for obtaining a lung biopsy specimen. Pentamidine isothionate is moderately effective against this usually fatal disease, but its effectiveness depends on beginning treatment early in the illness.

PNEUMOCYSTIS CARINII is an opportunistic protozoan which causes interstitial pneumonia. Originally, it was described as a disease of premature and marasmic infants, but it is now being reported with increasing frequency in patients who have been immunosuppressed and are immunodeficient.[1-4] With the rise in transplantation and use of chemotherapy, the number of immunosuppressed patients residing in local communities will increase. There they will run the risk of the initial symptoms of pneumocystis carinii pneumonia developing. Our particular concern is for the pediatric age group, in which the incidence of this disease is highest.[5] Since successful treatment depends on early diagnosis, it is important that clinicians be aware of this growing problem. This report of 13 pediatric cases emphasizes those factors that may aid in early diagnosis.

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Patients and Results of Therapy

Patients

From a search of medical records at the University of California, San Francisco, Medical Center from October 1971 to February 1975, we found 13 patients (nine boys, four girls), ranging in age from 6 months to 17 years, in whom the diagnosis of pneumocystis carinii pneumonia had been made (Table 1). Seven of eight patients with acute lymphoblastic leukemia were in hematologic remission when pneumocystis carinii pneumonia developed; five of them were in the one- to two-week period following prophylactic central nervous system treatment by irradiation or intrathecally given methotrexate (or both) and pred-

nisone withdrawal; two were within one week of termination of central nervous system prophylaxis; one had just finished a six-week course of vincristine and prednisone which did not produce remission. In two patients renal transplants had been carried out and immunosuppressive drugs were being given; one was doing well eight months after transplant when pneumocystis carinii pneumonia developed, in the other it developed two weeks after treatment was given for rejection of the transplant. One patient with systemic lupus erythematosus had been receiving steroids for ten years before development of the disease, another with combined immunodeficiency had been treated with antibiotics for frequent infections. A patient with neuroblastoma was in remission while on intensive chemotherapy but died suddenly at home following a short febrile illness. Postmortem examination established pneumocystis as the cause of death.

Deaths

Of the three patients who died (Table 1), one died unexpectedly at home two days after an intensive chemotherapy regimen for neuroblastoma was completed. In the two patients in hospital, the time between symptoms and therapy was 10 and 12 days. There was an initial improvement with pentamidine therapy, but on the fifth and seventh days of treatment, respectively, the patients became febrile and tachypneic again. No improvement at any time during treatment was shown on x-ray studies of the chest.

Admission to Hospital

At the time of admission to hospital (Table 2) all patients were febrile (median temperature, 38.8°C) and had elevated respiratory rates (median, 48 per minute). Rales, nasal flaring and intercostal retractions were present in three. Neither the leukocyte count (600 to 7,400 cells per cu mm; median 4,900 cells per cu mm) nor the absolute eosinophil count was elevated; this was not unexpected in these immunosuppressed patients. Studies of arterial blood gases consistently showed a depressed oxygen pressure (Po_2)—median, 46 mm of mercury—and a normal or slightly depressed carbon dioxide pressure (Pco_2)—35 mm of mercury; blood gas studies were not done in two patients. Chest roentgenographs on admission showed a bilateral diffuse reticular pattern in ten patients and bilateral bronchial thickening in one; another was read as normal. Characteristically, the infiltrates radiated from the hilar region in a butterfly pattern. As the disease progressed, the opacification of the lung fields increased.

TABLE 2.—*Concurrent Findings on Admission in 13 Patients with Pneumocystis Carinii*

Findings	*Number Patients*	
Clinical		
Fever		13
Nonproductive cough		10
Tachypnea		8
Laboratory		
Chest roentgenograph		12
Bilateral infiltrates	10	
Bronchial thickening	1	
Normal	1	
Leukocyte count normal		10

Symptoms

The most common symptoms were fever, tachypnea and a nonproductive cough which occurred from one to seven days before admission to hospital. Anorexia, diarrhea, vomiting and listlessness were reported in younger children, whereas older children presented with dyspnea and substernal pain. Tachycardia and signs of respiratory distress (nasal flaring, intercostal or suprasternal retractions) were also present, cyanosis less commonly. In spite of respiratory distress, there were no physical findings on auscultation of the chest in ten patients, although in three rales were present.

TABLE 1.—*Cases of Pneumocystis Carinii at the University of California, San Francisco, Medical Center, from 1971 to 1975*

Predisposing Condition	*Age (years)* <1	1-5	5-10	10-17	*Total Number Patients*	*Died*
Acute lymphoblastic leukemia	..	5	3	..	8	..
Renal transplantation	..	..	1	1	2	1
Systemic lupus erythematosus	..	..	..	1	1	1
Combined immunodeficiency	1	..	..	..	1	..
Neuroblastoma	..	1	..	..	1	1
TOTAL	1	6	4	2	13	3

Lung Biopsy

In 11 patients diagnostic open lung biopsy was carried out, without complication. The chest tubes in all were removed within 48 hours, and within 24 hours in nine. Cultures for bacteria, fungus and Mycobacterium tuberculosis were consistently negative. In three patients there were concurrent infections (Pseudomonas aeruginosa from an abdominal wound; Salmonella Dublin from a bone marrow aspirate; one otitis media which was not cultured). In one patient diagnosis was made on clinical and roentgenographic findings. In one the diagnosis was confirmed histologically, by examination of postmortem tissue. If touch preparations, stained with toluidine blue for quick identification were negative,[6] another touch preparation was stained with Grocott's modified methenamine silver stain for final diagnosis.

Treatment

Treatment had been delayed in two of the patients who died; in both, a concurrent infection was a factor in delaying the diagnosis of pneumocystis carinii pneumonia. In seven of the ten survivors clinical and roentgenographic improvement was seen in the first five days of treatment with pentamidine isothionate (4 mg per kg of body weight per day) for 10 to 14 days after initial diagnosis, and these patients became afebrile between the third and eighth day (median 5.5 days) of therapy. On x-ray films of the chest improvement was seen between the second and tenth day (median four days). One patient, because of nonresponsiveness to five days of pentamidine administration, was treated also with sulfadiazine (100 mg per kg of body weight per day) and pyrimethamine (1 mg per kg of body weight per day) and became afebrile; also, improvement was seen on roentgenograms within 24 hours. The respiratory rate was normal five days later. Supportive care for all patients involved oxygen therapy, hydration and administration of antibiotics when indicated. There were no adverse reactions to pentamidine therapy, except for considerable pain and subsequent muscle fibrosis in the younger children.

Discussion

Pneumocystis carinii pneumonia occurs almost exclusively in patients with impaired immune defenses. The epidemic form occurs in infants in nurseries, typically involving premature and marasmic infants; the sporadic form, found in the United States, occurs in patients who are immunosuppressed or have primary immunodeficiency, or both. The highest incidence is in children less than 1 year of age when primary immunodeficiency disorders are most frequent, and in children from 1 to 9 years of age when acute lymphoblastic leukemia is most frequent.[5] The onset of disease in the population under 1 year of age does not appear to be related to any predisposing factor other than the underlying disease. In contrast, the onset of disease in children 1 to 9 years old appears to be correlated with the intensity and stage of chemotherapy. From our experience and that of others,[1,2] the critical time for pneumocystis carinii pneumonia to develop is just after a period of intense immunosuppression.

Human transmission of pneumocystis carinii pneumonia is suggested by reports of cases in patients in hospital[7,8] and in family members[9] and by histologically[3] or serologically[10,11] proven pneumocystis infections in symptomatic persons. Since this disease is found in the lungs of a wide variety of asymptomatic animals, the possibility of an animal vector has been proposed but never proven.

This disease has been reported in children with pure humoral[12] as well as cellular immune deficiencies,[13] so that both immune mechanisms may be necessary for complete protection against overt illness. In immunosuppressed patients, this disease can exist as a dormant infection. The onset of overt illness appears to be related to the intensity of the immunosuppressive therapy: "less intense" therapy predisposes to dormant infections and "more intense" therapy to overt illness.[3]

Because of the nonspecific clinical manifestations, its successful diagnosis requires a high degree of suspicion and a knowledge of the population at risk. The most helpful aid is an x-ray study of the chest. In a study by Goodell and co-workers[4] the most frequent cause of bilateral diffuse reticular infiltrates in immunosuppressed patients with neoplastic disease was pneumocystis carinii pneumonia.

The diagnosis is made by histologic identification. Unfortunately, there is no satisfactory method for obtaining a reliable specimen for study. In our hands, lung biopsy has proven more reliable than sputum, tracheal aspirate, endobronchial brush biopsy or serologic tests. However, opinions are divided between open thora-

cotomy and percutaneous needle biopsy as the best method for lung biopsy. We use open thoracotomy because it has the highest yield of all diagnostic procedures (65 percent),[5] and allows for direct visualization of the lung, more certain selection of a diseased portion for biopsy,[14,15] and adequate tissue for bacterial, fungal and viral studies. We have had no postoperative complications, although they may be anticipated. While percutaneous needle biopsy, either the cutting or aspiration technique, has the advantage of subjecting the patient to less trauma, it has the disadvantage of a lower yield (51 to 55 percent) and the possibility of false-negative results.[5] The diagnosis also can be complicated by concurrent bacterial, viral and, less frequently, fungal infections, and drug-related lung pathology (from busulfan, cyclophosphamide, bleomycin and methotrexate) which is radiologically similar to that of pneumocystis carinii. A lung biopsy will help to resolve this dilemma.

Pentamidine isothionate[16] is an effective drug for the treatment of pneumocystis carinii pneumonia if given early in the illness and for nine or more days. In survivors in our series (ten of 13 patients) clinical improvement usually was seen by the fifth day of treatment, but roentgenographic improvement may not become evident for up to ten days, and several months may be required for complete resolution of pulmonary infiltrates. Reportedly, the most adverse reactions to pentamidine therapy are reversible azotemia, hypoglycemia, abnormal liver function and local reactions (pain, sterile abscess and ulceration) at the injection site.[16] In two of our patients there were local reactions which prevented them from walking for several weeks after treatment. Pentamidine is a toxic drug and every effort should be made to identify pneumocystis carinii histologically before initiating therapy with it.

Continued investigation of other agents for the treatment of pneumocystis pneumonia is warranted since the cure rate is only 70 percent and adverse reactions are common. Sulfadiazine and pyrimethamine are as effective as pentamidine in animal studies,[17] but their limited trial in human studies has not produced similar results.[18] A recent report[19] using trimethoprim and sulfamethoxazole in children with pneumocystis pneumonia of mild to moderate severity shows this combination to be effective and free of adverse effects. A study comparing its therapeutic efficacy with that of pentamidine seems justified. Recent animal studies also suggest that trimethoprim and sulfamethoxazole may be efficacious in the prevention of this disease.[20] Since pneumocystis pneumonia is most likely to occur just after a period of intensive immunosuppression, a controlled trial of prophylactic therapy may be of value.

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Medical
PROGRESS

Infectious Mononucleosis and Mononucleosis Syndromes

Clinical, Virological and Immunological Features

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Infectious mononucleosis (IM) and cytomegalovirus (CMV) mononucleosis are caused by a primary infection with related viruses, Epstein-Barr virus (EBV) and CMV. Despite the similarity of clinical manifestations, basic differences exist: (1) The heterophil antibody (HA) response is absent in CMV mononucleosis, whereas it is present in IM. (2) In IM atypical lymphocytosis reflects proliferation of B cells early and of T cells later in the disease course; in CMV mononucleosis the situation appears complex. (3) In blood, EBV is restricted to B lymphocytes, whereas CMV is found in polymorphonuclear and mononuclear leukocytes. (4) Complications of CMV mononucleosis such as hepatitis and pneumonitis may be due to virus cytopathic effect in target organs. Prominent tonsillopharyngitis with adenopathy, and visceral complications of IM are related to lymphoproliferation which is self-limited except in males with a rare familial defect in defense against EBV. Immune complex-mediated pathology may occur in both diseases. (5) CMV is frequently transmitted to a fetus in utero *or to an infant during or after birth, and this occasionally leads to severe cytomegalic inclusion disease; vertical transmission of EBV appears to be exceptional. (6) Secondary EBV infections are associated with certain malignancies whereas such an association has not been recognized in the case of CMV.*

Toxoplasma gondii is another cause of HA-negative mononucleosis. Its complications in the heart, in skeletal muscle and in the central nervous system are related to direct invasion by the parasite. Cellular immunity plays an important role in defense against all three agents.

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ABBREVIATIONS USED IN TEXT

CF = complement fixing
CMV = cytomegalovirus
EA = early antigen
EBNA = EBV-associated intranuclear antigen
EBV = Epstein-Barr virus
HA = heterophil antibody
IFA = indirect fluorescent antibody (test)
IHA = indirect hemagglutinating antibodies
IM = infectious mononucleosis
LFT = liver function test
MA = membrane antigen
NPC = nasopharyngeal carcinoma
VCA = virus capsid antigen

ACUTE FEBRILE DISEASES of adolescents and young adults accompanied by pronounced lymphocytic response are usually diagnosed as infectious mononucleosis (IM) or heterophil antibody (HA)-negative mononucleosis. IM is caused by a primary infection with Epstein-Barr virus (EBV).[1,2] HA-negative mononucleosis is due to EBV[3] or to cytomegalovirus (CMV)[4] and less commonly to Toxoplasma gondii;[5,6] beta-hemolytic streptococcus; Listeria monocytogenes; viruses such as adenovirus, hepatitis A, herpes simplex, rubella and mumps,[7] and reactions to para-aminosalicylic acid, diphenylhydantoin or isoniazid. Human herpesviruses including EBV and CMV,[8,9] and IM[10-12] have been extensively reviewed. This article deals with clinical, virological and immunological features of IM, CMV and toxoplasmic mononucleosis.

Infectious Mononucleosis

IM is an acute illness characterized by fever, pharyngitis, cervical lymphadenopathy, an absolute (greater than 4,000 per cu mm) and a relative (greater than 50 percent) increase of mononuclear cells in the peripheral blood, atypical lymphocytosis (greater than 20 percent of the total leukocyte count[13]) and abnormal findings on liver function tests (LFT). The differential HA test (Paul-Bunnell-Davidsohn test)[14] is positive in 90 percent of young adults with primary EBV infection.

Spectrum of EBV Infections[15]

In patients with IM, primary antibody response to EBV develops and thereafter immunity to IM is maintained for life. Typical IM develops when infection occurs in adolescence or young adulthood; in childhood most infections are subclinical or atypical. Among deprived socioeconomic groups, infection usually occurs in early childhood. Infection occurs in 12 percent of susceptible American and English freshman students, in 25 to 75 percent of whom IM develops.[16-19] The annual incidence of clinical IM is about 5 percent in susceptible students, but only one hundredth this figure in general population.

Secondary attack rate of IM in college roommates is about 5 percent[12] whereas, in well-to-do Swedish families, it was shown to be 33 percent.[20] The incubation period has been recorded at 30 to 45 days.[21] EBV is transmitted in saliva (IM is known as a "kissing disease"). Acquisition of IM without a known contact is explained by prolonged oropharyngeal excretion of EBV.[22-25]

Secondary EBV infections are associated with Burkitt's lymphoma, nasopharyngeal carcinoma, and possibly with the lymphocyte-depletion and mixed cellularity types of Hodgkin's disease.[26] Although the role of EBV in these malignancies is controversial, recent evidence suggests a causative rather than a passenger role.[26-32] The course of EBV infection may depend on the genetic susceptibility of the host,[33-36] the status of humoral and cellular immunity at the time of primary infection,[35,36] coexistent malaria,[37] an endogenous ribonucleic acid (RNA) tumor virus,[38] or involvement of virulent virus strains.[39-41] Susceptibility to IM is not linked to specific HL-A types;[42] however, increased frequency of HL-A2 at the first locus and a new antigen Singapore-2 at the second locus are associated with nasopharyngeal carcinoma.[43]

Manifestations and Laboratory Features

Following nonspecific prodromes the presenting symptoms are fever and sore throat which persist two weeks or more and are unresponsive to antibiotic therapy; lympadenopathy, jaundice or a transient maculopapular rash are less common presentations. Pharyngeal exudate is present in about half and streptococcal superinfection in a quarter of cases. Petechial enanthema on the soft palate is common. Lymphadenopathy lasting several weeks is a constant feature and involves posterior cervical nodes or is generalized. Splenomegaly and hepatomegaly are frequently present and in most patients findings on liver function tests are abnormal.[44] Involvement of the lymphoreticular system may cause abdominal pain. Atypical lymphocytes ("Downey" cells[45]) have been classified as: Type I—about the size of small lymphocyte with clumped chromatin and sharply defined parachromatin; Type II—larger cell with "smudged" chromatin; Type III—large

cell with royal blue cytoplasm, open chromatin and a prominent nucleolus.

In children EBV infection should be suspected when a febrile illness is accompanied by atypical lymphocytosis (absolute lymphocytosis with 3 to 10 percent atypical lymphocytes is normal before the age of 6), lymphadenopathy, and splenomegaly or hepatomegaly, often without an HA response.[46] Severe complications, including Reye's syndrome, may occasionally occur in the absence of typical features of IM. A high antibody titer to virus capsid antigen (VCA) and a low complement-fixing (CF) antibody titer supports the diagnosis of a primary EBV infection in childhood.[47] In young adults, the ratio of clinically manifest (including respiratory symptoms only) to subclinical disease is about 2 to 1.[19] The disease is rare in middle age but tends to be severe. Symptoms may recur in patients responding late to the restricted (R) component of the early antigen (EA) complex.[48]

Complications

IM is usually a benign illness. The most frequent complication has been hypersensitivity following treatment with ampicillin or penicillin (95 percent and 44 percent, respectively, of those receiving the drugs[49]), as a maculopapular rash which is of greater severity than the "spontaneous" rash. This reaction does not imply permanent hypersensitivity to either drug.[49-52]

Hemolytic anemia occurs in rare instances one to two weeks after the onset of IM and is thought to be due to anti-i agglutinin (rarely anti-N agglutinin[53]) in a high titer[54] and active over a wide thermal range.[55,56] Red cells may be converted from the adult I antigenic form to the fetal i form.[53,57] Cold agglutinins are usually IgM but IgG agglutinins[58] may be found which act in conjunction with a cold-reactive IgM antibody against IgG.[59,60] The direct Coombs test may be positive using antiglobulin, anti-C3 or anti-C4 reagents. Anemia is usually due to extravascular hemolysis but intravascular hemolysis may occur in severe cases.[53,61] Patients with spherocytosis, thalassemia or congenital pyruvate kinase deficiency develop increased hemolysis during stress including IM.[62] Some IM patients have increased autohemolysis which correlates with spherocytosis and elevated mean corpuscular hemoglobin concentration suggesting occult hemolysis.[63] Hypersplenism of chronic infection[64] or bone marrow depression[53] may be seen.

Although thrombocytopenia and abnormalities of platelet function are common, thrombocytopenic purpura is rare. Antiplatelet antibodies[65] and anti-i agglutinins (platelets carry the i-antigen)[66] appear to be of pathogenic significance. In some patients disseminated intravascular coagulation with hypofibrinogenemia may contribute to bleeding.[67] IM presenting with lymphopenia is exceptional and tends to have severe complications.[68] Severe neutropenia,[69-71] and very rarely pancytopenia,[72] may arise several weeks after the onset of IM. Neutrophils have low alkaline phosphatase content during the first week of illness.[69]

Lymphocytic infiltration results in visceral complications. The prognosis in carditis[73,74] and most other complications is generally good but rupture of the spleen; neurological complications; respiratory obstruction; lymphoproliferative or pancytopenic disorders, and secondary hypergammaglobulinemia or agammaglobulinemia may be fatal.[75-77] Acute nephritis occurs in as many as 13 percent of patients[78] in the form of either an interstitial nephritis with tubular atrophy or a mesangial proliferative glomerulonephritis. Interstitial mononuclear infiltrates distinguish mononucleosis from poststreptococcal nephritis.[79] Hemolytic uremic syndrome followed IM in one 14-year-old boy.[80]

Hepatitis is mild and the abnormalities on LFT's reflect the degree of infiltration of portal tracts by mononuclear cells and of hepatocyte necrosis.[81] Intense hyperbilirubinemia may result from a combination of hepatitis and hemolytic anemia.[82] Fatal hepatic necrosis is rare.[83,84] The ultrastructure of liver cells in hepatitis shows dilation of the endoplasmic reticulum[85] and, in the presence of hepatic necrosis, margination of chromatin and herpes-like virions.[84] A transient malabsorption is associated with thickened jejunal folds, which are infiltrated with large lymphocytes.[86] Diabetes mellitus may have a fulminant onset during IM.[87] Upper respiratory obstruction is a serious complication.[88] Interstitial lung infiltrates may be followed by Hemophilus influenzae or Staphylococcus aureus superinfection, pleural effusion,[89] or septicemic features.[90]

Neurological complications include encephalitis[91] occasionally with focal manifestations,[92] acute cerebellar syndrome,[93] aseptic meningitis, Guillain-Barré syndrome,[94] transverse myelitis, asymmetrical brachial neuropathy (mononeuritis, mononeuritis multiplex,[95] neuralgic amyotrophy —shoulder-girdle syndrome—or radiculopathy),

Bell palsy,[96] and Reye syndrome.[97,98] The incidence of neurological complications is less than 1 percent[99,100] and these may occur at any time, but usually one to three weeks after onset of IM.[101] Atypical lymphocytes, HA and EBV antibody in the spinal fluid[93] suggest that the virus directly involves the nervous system but a demyelinating process also occurs.[92] In one study, a third of young patients with Guillain-Barré syndrome and a third with Bell palsy were associated with a recent primary EBV infection, although they were without clinical signs of IM or HA response.[102] Chorioretinitis has been reported in a few cases.[103]

The relationship, if any, among lymphoma, leukemia and EBV is not clear.[104-112] In one 16-year-old boy a mononucleosis-like illness progressed to a fatal generalized lymphoproliferative disorder of B-type. EBV infection was shown to be present by the finding of herpes virions in

TABLE 1.—*Serological Findings in Two Types of Mononucleosis*

	Infectious Mononucleosis		*CMV Mononucleosis*	
	Finding	*Reference*	*Finding*	*Reference*
Antibodies				
Heterophil	Rise (90% of adults, uncommon in children)	(2,128)	None	(3,182)
to Epstein-Barr virus (EBV) capsid antigen (IgG antibody) (measured by immunofluorescence [289] or radioimmunoassay [290])	High, rising or falling titer of antibody	(128)	No change; except in rare dual infections	(3,182)
to EBV capsid antigen (IgM antibody)	High, and after 2-3 months falling titer	(126)	Weak cross-reaction	(127)
to EBV early antigen (EA) (including responses to diffuse [D] and restricted [R] type antigens)	Rise of antibodies to diffuse antigens (in 70-80% patients)	(128,291)	?	
	rise of antibodies to restricted antigens in 16%	(48)	?	
EBV complement-fixing (CF)	Late rise (7th month after onset)	(130,131)	?	
to EBV nuclear antigen (EBNA)	Late rise (1-6 months post onset)	(29,128)	?	
EBV neutralizing	Early rise	(292)	?	
Cytomegalovirus (CMV) complement-fixing	No change	(3,184)		
	(except in rare dual infections)	(185,223)	Rise (peak 4 to 7 weeks after onset)	(3,4)
to CMV intracellular antigens (IgG antibody detected by immunofluorescence)	No change	(128)	High or rising titer	(184)
to CMV intracellular antigens (IgM antibody detected by immunofluorescence)	Extensive cross reactions	(240)	Present at least 2 to 8 months	(192,241)
	(some due to rheumatoid factor)	(241)		
to CMV soluble antigens (indirect hemagglutinating antibody)	?		Rising titer	(236)
CMV neutralizing	Rise (test done in presence of complement)	(244)	Rising titer	(4,244)
to CMV early antigen	?		Antibody rise (peak 10 to 19 days after onset)	(246)
to CMV nucleocapsid	.....	....	Antibody rise (1 to 2 weeks post onset)	(245)
to CMV enveloped virions	.....	....	Antibody rise (4 to 6 weeks post onset)	(245)

lymph nodes, EBV deoxyribonucleic acid (DNA) in the spleen and by HA. There was failure to produce antibody to EBV in the patient and leukocytes were not stimulated by phytohemagglutinins. Three male relatives died from a similar disorder.[113] In another family, three males had an acute illness with adenopathy and hepatosplenomegaly which was fatal in one patient, whereas in the other two agammaglobulinemia developed.[114] In a third kindred, six of 19 boys died of a disorder characterized by proliferation of lymphocytes and histiocytes, either hyper- or agammaglobulinemia, and by certain features of IM.[77]

Differential Diagnosis

The following are differential diagnoses:

- HA-negative mononucleosis;
- The exudative pharyngitis caused by bacterial or other viral pathogens, or occurring in acute leukemia;
- Pronounced lymphocytosis accompanying pertussis and acute infectious lymphocytosis; moderate lymphocytosis in certain chronic bacterial and in many acute viral infections;
- Prodromal arthralgia, skin rash and elevated serum transaminase and bilirubin of hepatitis A and B (serum transaminase and bilirubin levels are higher in viral hepatitis than in IM;[115] alkaline phosphatase is elevated in both diseases, but in patients with IM there is a dissociation between elevated alkaline phosphatase and serum glutamic oxaloacetic transaminase, and a low bilirubin level[116]);
- Systemic diseases, infective endocarditis, lymphoma and acute leukemia resemble the "typhoid" course of IM.

Serology and Immunopathology

Serological and immunologic findings are shown in Tables 1 and 2.

HA agglutinating sheep red cells are found in patients with IM at a titer of 1:112 or greater whereas usually low titers occur in cases of malignant lymphomas, sarcoidosis,[117] rheumatoid arthritis,[118] viral respiratory infections and serum sickness. The differential HA test is specific for IM when the titer is decreased 8-fold or less by absorption with guinea pig kidney but decreased 16-fold or more following absorption with beef erythrocytes.[14] Horse erythrocytes allow a sharp differentiation between IM agglutinins and non-

TABLE 2.—*Immunologic Aberrations in Infectious and Cytomegalovirus Mononucleosis*

	Estimated Incidence (Infectious Mononucleosis) Percent*	*Reference*
Auto- and isoantibodies		
Cold agglutinins (usually with anti-i specificity)	8- 79	(54,202)
Rheumatoid factors		
a. warm-reactive	10	
b. cold-reactive	72	(293)
Antinuclear antibodies (transient)	66	(294)
Cryoglobulins (transient, mixed IgG and IgM)	95	(295)
Venereal Disease Research Laboratories test (biological false positive)	19	(294,295)
Donath-Landsteiner haemolysin	?	(140)
Antilymphocyte	100	(142-144)
Antiplatelet	?	(65)
Antismooth muscle	44- 81	(141)
Antimicrotubules	81	(145)

	Infectious Mononucleosis	*Reference*	*Cytomegalovirus Mononucleosis*	*Reference*
Lymphocytes				
Atypical lymphocytes in peripheral blood	B lymphocytes elevated for 1-3 weeks (max. 1st week); T lymphocytes elevated for 5 weeks (max. 2nd week)	(150)	Atypical lymphocytes elevated for weeks to months	(4)
			T cells increased	(148)
			or nul cells increased	(185)
Immunosuppression				
of humoral immunity	?	....	in one case	(185)
of cellular immunity	100 percent	(150)	in one case	(185)

*The incidence in cytomegalovirus mononucleosis is not known precisely.

IM agglutinins (which are reduced equally or to a greater degree by absorption with guinea pig kidney than with beef red cells).[119] The slide agglutination test[120] using citrated horse erythrocytes has optimum sensitivity whereas a beef hemolysin test appears the most specific.[121] It is not clear whether HA arises as a response to common antigens on sheep erythrocytes and EBV-transformed cells,[122] or through another mechanism.[123]

Antibodies appear in the following sequence: (1) In the incubation period, IgM and IgG antibodies to VCA and EA; (2) in the acute phase, EBV neutralizing antibodies and antibodies to membrane antigen (MA), and HA; (3) in the convalescent phase, antibodies to CF antigen and to EBV-associated intranuclear antigen (EBNA). The following findings are characteristic of IM:

- IgM antibody to EBV;[124-126]
- IgG antibody to VCA in a titer of at least 1:320, or a rising or falling titer;
- Transitory response to the diffuse (D) component of the EA complex (present in 85 percent of patients);[127] 15 percent of patients respond in late convalescence with anti-R (restricted component) antibodies and tend to have a complicated course;[48]
- Late rise of CF and anti-EBNA antibodies;[127-131]
- Isolation of EBV from the throat indicates either a recent or a remote infection;[23,132]
- Peripheral leukocytes from patients with IM rapidly establish permanent lines *in vitro*[133] (*in vivo* some EBV exists in a nonproductive state[134]); EBNA is found in about 1 percent of peripheral B lymphocytes [Jondal, M., personal communication]).

IgM, IgG, IgA[135] and, in some patients, IgE and IgD[136] immunoglobulins are elevated by as much as 100 percent, yet less than 5 percent can be accounted for by HA or anti-i antibody.[137] Iso- and autoantibodies in IM include: cold agglutinins, rheumatoid factor, antinuclear factor,[138] Wasserman antibody, Donath-Lansteiner cold hemolysin,[139] and antibodies to erythrocytes, platelets, smooth muscle,[140] lymphocytes,[141] subpopulations of T- and B- lymphocytes[142,143] and cytoplasmic microtubules.[144] IgM-IgG cryoglobulins may contain some of these antibodies[145] in addition to EBV VCA antibody, virions and components of the classical and alternative complement pathways.[146]

The atypical lymphocyte has been thought to be of T-cell origin.[147-149] Findings in recent studies suggest that B-cells proliferate mainly during the first week of illness whereas T-cells do so thereafter.[150-152] This may result from an initial viral invasion of B-cells (*in vitro* EBV grows only in B-cells[153-156]), induction of viral antigens in B-cells and a subsequent cytotoxic response by T-lymphocytes.[149,150,157-163] Antibodies to EBV MA may also control lymphoproliferation.[164] During IM there is depressed lymphocyte response to various mitogenic and antigenic stimuli, and dermal anergy.[150] The depression may result from suppression of responder T-cells by suppressor T-cells or as a result of responder cells releasing a negative mediator.[165,166]

Histopathological changes in lymph nodes involve a mixed proliferation of small and large lymphocytes, plasma cells, "immunoblasts" (large cells with sharply demarcated nuclei containing loose chromatin and two nucleoli, and a pyroninophilic cytoplasm) and blood vessels. Binucleate "immunoblasts" resemble Reed-Sternberg cells and may lead to an erroneous diagnosis of Hodgkin disease.[167] In more advanced stages distortion of normal architecture with lymphoid infiltration of the capsule is found.[167-169] Atypical lymphocytes infiltrate the spleen, especially in the red pulp and sinusoids. The follicles contain eosinophilic material which includes damaged arterioles plus exuded proteins.[170] In the sternal bone marrow, pronounced hyperplasia may simulate malignant transformation.[171]

Treatment

Treatment of uncomplicated IM is symptomatic. Most patients recover in five weeks or less. Orally given prednisone or intravenously given hydrocortisone is indicated for severe respiratory or central nervous system involvement, thrombocytopenic purpura with hemorrhage, hemolytic anemia or severe hepatitis.[172,173] Splenectomy has occasionally been required for treatment of steroid-resistant thrombocytopenia.[174] Transfusions should be administered at 37°C to avoid cold agglutination.

Cytomegalovirus Mononucleosis

CMV mononucleosis, which is caused by a primary CMV infection, has many features similar to IM but there is no HA response. It occurs either "spontaneously" (CMV may be transmitted by oral route or venereal contact[175]) or after blood transfusion.

Epidemiology

In childhood, subclinical and minor respiratory, gastrointestinal and hepatitic forms of CMV infection are common.[176,177] Typical CMV mononucleosis occurs in subjects over 20 years of age.[176,178,179] CMV antibody is acquired at an earlier age in subjects of low-economic status.[180-182] There are also geographical differences. In Japan subclinical infection occurs in 60 percent of infants by 5 months of age.[183] Among 200 Finnish patients with mononucleosis, CMV was associated with 19 of 44 heterophile-negative cases.[3] Among 411 Swedish patients with mononucleosis, CMV was involved in approximately 20 of 300 HA-negative illnesses. In four patients there were dual CMV and EBV antibody rises.[184] The transmission of CMV depends on prolonged shedding of virus in the throat,[176,185] or in the urogenital tract including semen.[186,187] Postransfusion mononucleosis may occur at any age. The incubation period is one to three months. The following is relevant to virus transmission during transfusion and cardiopulmonary bypass:

- The risk of seroconversion is related to the volume of transfused blood but not to the level of preexisting CF antibody;[188]
- CMV had been found in cultured leukocytes of certain healthy blood donors[187] although subsequent studies[190,191] have not confirmed this;
- Some cases of posttransfusion mononucleosis result from a primary infection[192] whereas reactivation of a latent infection is thought to occur when there is evidence of a previous CMV infection;[193] the stress imposed by cardiopulmonary bypass may facilitate reactivation of a chronic infection.[194]

Clinical and Laboratory Features

Finnish patients with "spontaneous"[4] and posttransfusion CMV mononucleosis[195] had fever for two to five weeks, minimal or absent tonsillopharyngitis, and adenopathy. Initial leukopenia was followed by lymphocytosis with abundant atypical lymphocytosis which persisted for at least two weeks. Mild abnormalities on LFT's and, in a few patients, hepatomegaly, vestibular and cochlear involvement, arthralgia, skin rash, pneumonia and cold agglutinins were also found.[196] Some Swedish patients had conjunctivitis, vaginitis, severe headache and abdominal pains.[178] All of nine American patients[197] had prolonged fever, fatigue, myalgia and mild sore throat; two had generalized lymphadenopathy and three splenomegaly. In one patient Guillain-Barré syndrome developed and in another splenic infarction. Fever relapsing over many months was a particular feature in German patients.[198]

Complications

Ampicillin-induced skin rash,[199] hepatitis and polyneuritis are the most frequent complications of CMV mononucleosis in normal subjects. Less common complications include congenital disease in the offspring,[200] endometritis,[201] thrombocytopenia, hemolytic anemia,[202] interstitial pneumonitis,[203] myocarditis and pericarditis,[204] inflammation of pancreatic islets,[205] acute onset diabetes,[206] epidermolysis[207] and meningoencephalitis.[208] In immunologically impaired patients, CMV has been related more often to severe manifestations than in normal subjects,[209] including high spiking fever, arthralgias, pneumonitis, hepatitis and retinitis.[210-212]

Factors determining virus transmission and pathogenicity in the fetus are poorly understood. Congenital CMV infection is common (0.5 to 1.5 percent incidence[213]), but in most cases patients are asymptomatic at birth. There is a high level of immunity and of cervical shedding of CMV in women of childbearing age in some communities (in Alabama 89 percent of women had antibody and 11.3 percent shed virus during the third trimester).[214] Also some mothers have consecutive congenitally infected infants.[215] These findings suggest that primary gestational infections cannot explain all congenital infections. It is, however, conceivable that the severe congenital disease results from primary maternal infection in the first[200] or second[216,217] trimester.

Hematological complications of CMV mononucleosis include hemolytic anemia[202] and thrombocytopenia.[218,219] Thrombocytopenia may be severe and not respond well to splenectomy or to steroids.

Although mild liver involvement is common, severe hepatitis due to CMV is rare.[185,220,221] Findings on liver biopsy show periportal mononuclear or mixed cell infiltrates occasionally accompanied by Kupffer cell hyperplasia and focal necrosis of liver cells. Inclusion-bearing hepatocytes[222] and bile stasis[84] are also found. Rarely cholestatic jaundice with substantial elevation of bilirubin and alkaline phosphatase and with liver granulomas is found.[223]

CMV infection was associated with acute inflammatory disorders of the central nervous system in

two Finnish patients[224] and of the peripheral nervous system in English patients.[206] CMV was incriminated in more than a third of 80 American cases of acute polyneuritis.[225] Vestibular and cochlear involvement may occur in CMV mononucleosis.[4] Although most complications are benign, in one patient myocarditis, encephalitis, hepatitis and adrenal insufficiency developed and the patient died from congestive heart failure.[226] In another, carditis and hepatitis were followed by disseminated intravascular coagulation and shock.[227]

Immunopathology

Immunologic findings are shown in Table 2.

Cold agglutinins, rheumatoid factor, antinuclear antibodies, mixed IgM and IgG cryoglobulins (rich in antinuclear antibodies, rheumatoid factor or cold agglutinins),[146] and erythrocyte autoantibodies may develop in mononucleosis.[202] In a patient with acute leukemia, CMV mononucleosis and a transient monoclonal gammopathy of IgA-lambda type developed.[228] It is conceivable that arthralgia[196,212] and glomerulitis[229] in infected patients result from deposition of immune complexes. Some cases of hemolytic anemia could be a consequence of occult infection of the reticuloendothelial system.[230] The origin of atypical lymphocytes is not clear but, in one case of CMV mononucleosis, increased numbers of T-cells were found,[148] whereas, in another case, increased null cells were observed.[185]

Serology

Table 1 shows serologic findings.

With the use of a broadly reactive CF antigen from the strain AD 169, antibody response is detected in nearly all primary CMV infections except in infants.[231-233] This antibody is specific[234] and is largely of the IgG class. In some infected subjects,[212,235] the titer of antibody may have declined below 1:8 at the time of reinfection giving an impression of a primary infection. Indirect hemagglutinating antibodies (IHA) of IgM and IgG classes[236] rise earlier and to higher titers than CF antibodies. Immunofluorescent IgG antibody titers generally parallel those of IHA. Neutralizing antibody is slow to appear,[237] and displays strain specificity.[238,239] Immunofluorescent IgM antibody is found in recent infections.[192,240-242] False-positive IgM reactions may result when IgM rheumatoid factor-like antibodies attach to antibodies of the IgG class. This can be circumvented by preabsorbing the serum with aggregated gamma globulin.[243] Antibodies determined by complement fixation tests using enveloped virions develop several weeks later than those reacting with nucleocapsids.[244,245] Immunofluorescent antibody to an early antigen (EA) peaks later than the immunofluorescent IgG antibody and is absent from sera of healthy subjects seropositive in the CF test.[246]

Cytomegalovirus Viremia and Excretion

In viremic blood, infectious CMV is carried predominantly in polymorphonuclear leukocytes and, at low titer, in the mononuclear leukocyte fraction[202] where it may reside in monocytes (Fiala, M. and Saxon, A., unpublished). Mouse CMV is associated with B-lymphocytes in both latent and productive infections.[247] A lymphoblastoid line derived from peripheral leukocytes of a child congenitally infected with CMV is persistently infected with EBV and CMV.[248] B-cell lines carrying EBV can be abortively superinfected with CMV.[249] CMV stimulates host-cell deoxyribonucleic acid (DNA) synthesis in permissive as well as nonpermissive cells[250] and transforms hamster embryo fibroblasts.[251] In man, CMV viremia may be transitory when it results from phagocytosis of virus by polymorphonuclear leukocytes or monocytes, or both; or it could represent a stable association of virus with lymphocytes with a possibility of oncogenic interactions.

Treatment and Prophylaxis of Cytomegalovirus Infections

No specific therapy is usually indicated. Experimental treatment with adenine arabinoside[252] resulted in a temporary decrease of CMV excretion without any effect on the clinical course.[253] An experimental live vaccine is immunogenic in man,[254] but it is of unproven value at present.

Toxoplasmic Mononucleosis

Toxoplasmosis—Clinical Spectrum

Infection with the protozoan parasite Toxoplasma gondii may be asymptomatic (most cases) or cause a variety of manifestations. The most common feature of postnatal infection is lymphadenopathy, in some cases associated with fatigue, malaise, fever, hepatomegaly, splenomegaly, lymphocytosis and the presence of atypical lymphocytes. The HA test is negative and specific serologic tests for toxoplasmosis are positive. Congenital infection may occur when the mother

acquires the disease during pregnancy. Chronic toxoplasmosis may cause retinochoroiditis.

Etiology and Epidemiology

Toxoplasma is now classified among the coccidian parasites.[255] The organism has been recovered from a wide variety of mammals and birds, but one phase of its complex life cycle is unique to cats and other felids. In cats, intestinal epithelial cells are parasitized by asexual and sexual forms and oocysts are excreted in the feces. Oocysts become infective within one to several days after they are shed. Humans are incapable of developing the intestinal infection but harbor two forms of the parasite, the proliferative form (endozoite, tachyzoite) and the tissue cyst. The proliferative form is ovoid with a slightly tapered anterior end and measures 4 to 7 μ by 2 to 4 μ. It is able to penetrate and multiply in nearly all types of nucleated cells. Reproduction occurs by endodyogeny;[256] that is, the development of two daughter cells within the parent cell. The tissue cyst (30 to 60 μ in diameter) has a thin wall and may contain more than 3,000 individual organisms (cytozoites, bradyzoites).

Toxoplasma cysts have been demonstrated in mutton, pork and beef,[257] and clinical disease[258] and seroconversion[259] have been shown to follow the ingestion of raw and inadequately cooked meat. Domestic cats appear to be a major source of human infection.[260,261] Oocysts from cat feces are highly infectious and, under favorable conditions, may remain viable for many months to years. The prevalence of toxoplasmic antibody in humans is greater in warm, moist climates than in colder, dry areas and increases with age.[262] Approximately a fifth of young American adults are seropositive. Transmission has also occurred by accidental inoculation in the laboratory,[263] by organ transplantation[264] and by blood transfusion.[265]

Manifestations

The incubation period is estimated at 8 to 13 days for infections acquired by meat ingestion,[258] and 3 to 10 days for infections acquired in the laboratory.[263] Asymptomatic lymph node enlargement is the most common manifestation of acquired toxoplasmosis.[266,267] The lymph nodes of the head and neck are most frequently involved but generalized adenopathy occurs. A series of 38 patients with acquired toxoplasmosis[268] were found to have the following symptoms: lymphadenopathy (90 percent of patients), fatigue and malaise (40 percent), fever (37 percent), sore throat (21 percent), headache (18 percent), symptoms of myocardial disease (11 percent), retinochoroiditis (5 percent) and seizures (2.5 percent). Physical findings showed lymphadenopathy, usually posterior cervical nodes (97 percent), splenomegaly (32 percent), nontender hepatomegaly (32 percent), a maculopapular rash (11 percent) and erythema of the pharynx (8 percent). Atypical lymphocytes were present in 20 percent of the patients. The rash is maculopapular, nonpruritic and generalized, but usually spares the palms, soles and scalp. Dramatic cutaneous manifestations resembling a rickettsial infection are rare.[269]

Complications

Lymphadenitis usually resolves spontaneously over a period of weeks to months. Myocarditis, pericarditis,[270,272] pneumonitis[270] or myositis[273,275] may occur if the strain of parasite is particularly virulent or the immunologic responsiveness of the patient is impaired. Hepatitis,[276] glomerulonephritis[277] and interstitial nephritis[278] have been reported. In patients with impaired immunity, toxoplasmosis may cause severe central nervous system disease, encephalitis or a mass lesion, and myocardial and pulmonary invasion.[279-281]

Differential Diagnosis

Toxoplasmosis should be considered in the HA-negative mononucleosis syndrome. Lymphadenopathic toxoplasmosis may also mimic various forms of lymphoma. Central nervous system toxoplasmosis must be differentiated from disease due to other infectious agents, hemorrhage, cerebral or dural tumor, and progressive multifocal leukoencephalopathy.

Immunopathology

Cellular immunity appears necessary for complete protection of the host.[282] Corticosteroids, which suppress cellular defense mechanisms, predispose to infection. The lymphadenopathy of toxoplasmosis is attributed to hyperplasia of lymphoid tissue as part of the immune response.[283] Hypersensitivity of the delayed type results in necrosis in the vicinity of ruptured Toxoplasma cysts. Renal involvement may be due to immune complex nephritis.[277]

Diagnosis and Serology

Toxoplasma organisms may be recovered from infected tissue and body fluids by animal inocula-

tion or by tissue culture,[284] and may be shown to be present in tissue sections or impression smears by stains and by immunofluorescence. Histopathology of lymph nodes is diagnostic.[285]

The Sabin-Feldman methylene blue dye test[286] is specific and sensitive and has remained the reference standard for newer tests. Other useful serologic tests are the indirect hemagglutination test, the indirect fluorescent antibody test (IFA) and the complement fixation test.[284] Dye test antibody becomes detectable within one to two weeks after infection and the indirect hemagglutination test two to three weeks after infection, and both tests remain positive for life. The CF test is of value in determining the stage of infection as it becomes positive much later than the dye test. The IFA correlates well with the dye test, but false-positive reactions have been noted in the presence of antinuclear antibody.[284] Antibodies of the IgM class are detected by immunofluorescence (IgM-IFA test).[279-287] Acute infection is suspected when the IgM-IFA test becomes positive, even at low titer, and a dye test or IFA test has a titer of 1:1,000 or greater in a patient with compatible clinical manifestations. Acute infection is confirmed by IgM-IFA test of 1:600 or greater and a dye test or IFA test of 1:16,000 or greater.

Treatment

Toxoplasmosis without systemic involvement requires no treatment. Complications of toxoplasmosis may be treated with the combination of pyrimethamine and sulfonamides. Folinic acid and yeast will prevent the hematopoietic toxicity associated with pyrimethamine.[288]

Addendum

Since the termination of the literature search in February 1976, several important contributions have been reported. EBV in oral secretions has been found to be cell free and probably replicated in the parotid gland.[296] In Uganda, neonatal or perinatal infections with EBV, together with a heavy malaria burden or other stresses in early life, might be important determinants in the pathogenesis of Burkitt lymphoma.[297] EBV has been associated with encephalitis, in some cases even in the absence of heterophil response, by the titers of EBV antibodies.[298] Under crowded conditions, EBV may cause an outbreak of IM.[299] Elderly patients with IM tend to have a severe course with pronounced liver involvement.[300] The role of CMV in granulomatous hepatitis with lymphocytosis has been confirmed in two adults.[301] Murine CMV has frequently been used as a model of human infection. Thrombocytopenia occurs in both infections. Lymphoid cell necrosis, thymic atrophy, growth retardation and immune deficiency have been shown to occur in infected newborn mice.[302] Recently a primary CMV infection during the period after renal transplantation has been suggested as a possible factor in severe opportunistic infections of renal allograft recipients.[303] With the realization of CMV-associated morbidity in transplant patients, there is a renewed interest in the development of a CMV vaccine.

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Drugs and Diet as Causes of Vascular Headache

The first thing I'm interested in when I treat a patient with repetitive vascular headache is to find out if there's something that can be stopped, rather than something that I have to start therapeutically. . . . The first thing I'm sure to look for, and most of these patients are women, is whether or not they're receiving some type of estrogen treatment. . . . The majority taking birth control pills will have an increase in headache if they have a predisposition to vascular headache. This was more of a problem with the high-dosage forms of estrogen that were earlier available and they're less of a problem now; but they continue to be a problem. I know of no birth control pill on the market which is safe from the point of view of not aggravating migraine and occasionally producing stroke. . . . One can say exactly the same thing for postmenopausal replacement therapy. There are other drugs . . . that seem to be capable of aggravating vascular headache. The whole amphetamine group and, in some instances, the antihistamines are culprits. . . . There are clearly some patients in whom headache develops from dietary factors. The two common ones are the nitrites used to redden hot dogs, and tyramine. Now whether you go on from there to eliminate all milk products from the diet . . . remains to be examined, and I'm not sure that that has any real value. I'm more impressed by the common relationship of so-called functional hypoglycemia to migraine. If one wants to study migraine and precipitate an attack in a susceptible person, the best thing to do is to fast them all night and then give them a glucose tolerance test; and after about five or six hours, they'll get a lovely migraine headache for you as they get into a reactive type of hypoglycemia. If patients are instructed to reduce the amount of carbohydrate in their diet and to eat more lipid and protein and to stay away from starchy foods, they may experience a modest reduction in the frequency of headache. . . . I'm absolutely convinced that mild degrees of hypertension can be another important cause of vascular headache. . . . Patients with any kind of chronic pain, including intractable headache, tend to become depressed; and often, the only subtle symptom pointing to depression is early wakening in the morning with inability to get back to sleep. The trial of these patients on imipramine hydrochloride (Tofranil®) or amitriptyline hydrochloride (Elavil®) for periods of time in sizable doses, 25, 50 or 75 mg at bedtime once a day over weeks or months will result in considerable improvement in vascular headache.

—STANLEY VAN DEN NOORT, MD, *Irvine, CA*

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Specialty Conference

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ALLEN D. JOHNSON, MD

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The Medical and Surgical Management of Patients with Aortic Valve Disease

—A Symposium

ALLEN D. JOHNSON, MD:* *The proper management of patients with aortic valve disease provides a multitude of challenging clinical problems, and the nature of cardiac adaptations to the hemodynamic and mechanical burdens imposed upon the heart by disorders of the aortic valve has been a continuing topic for clinical and laboratory investigations. Aortic stenosis and aortic regurgitation represent distinctly different mechanisms of cardiac adaptation to pressure and volume overload, respectively, of the left ventricle; the hemodynamic abnormalities, clinical course and management of these two disorders, therefore, should be considered separately.*

In recent years, it has become evident that isolated aortic stenosis usually occurs in a setting other than chronic rheumatic valvulitis.[1,2] *In patients from adolescence through the sixth decade, congenital abnormalities of the aortic valve—particularly bicuspid and occasionally unicuspid valves—are responsible for most cases of significant isolated aortic stenosis (Figure 1). In this context, it is important to note that prevalence of a congenitally abnormal aortic valve is estimated to be between 0.7 percent and 2 percent of the United States population.*[3] *This prevalence indicates that aortic stenosis will continue to be a frequently encountered clinical problem. In patients over the age of 65, calcific aortic stenosis can develop on a previously normal aortic valve (Figure 2) apparently associated with atherosclerosis, perhaps hypertension, aging and associated degenerative processes;*[2] *the incidence of this form of acquired calcific aortic stenosis is unknown.*

Isolated aortic regurgitation, on the other hand, has multiple causes, can present acutely often accompanied by severe symptoms, or as a chronic process with ample time for accommodation of the left ventricle to the inposed volume overload. In contrast to aortic stenosis, where the natural history is reasonably well-defined and the onset of

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clinical symptoms is the major indicator for surgical intervention,[4] the natural history of chronic aortic regurgitation is more variable and the onset of myocardial deterioration commonly occurs before the onset of symptoms. Identification of early myocardial decompensation in chronic aortic regurgitation remains one of the major unsolved dilemmas in modern cardiology.[5,6]

In this specialty conference, we will attempt to correlate current knowledge of the natural history and pathophysiology of these disorders with rational approaches to their medical and surgical management, including use of important information gained from the history, physical examination, and noninvasive and invasive diagnostic techniques. Drs. Kirk Peterson and Jack Tsuji will begin this conference with a discussion of the hemodynamic abnormalities and cardiac adaptations encountered in aortic stenosis and aortic regurgitation.

ABBREVIATIONS USED IN TEXT

LVET = left ventricular ejection time
LVET index = LVET corrected for heart rate and sex, using appropriate regression equations
Vcf = velocity of circumferential fiber shortening
V max = maximal velocity of contractile element shortening

Figure 1.—Photograph of a congenitally bicuspid aortic valve that has become thickened, calcified and stenotic. A commissure extends to the aortic wall dividing the valve into two cusps.

Figure 2.—Severely stenotic, calcified aortic valve with three equal cusps. (Pathology specimen courtesy of Georgetown University.)

Myocardial Adaptations in Aortic Valve Disease

KIRK L. PETERSON, MD,* and I. JACK TSUJI, MD†

AORTIC STENOSIS causes a progressive pressure overload on the left ventricle as absolute or relative valve orifice size decreases and impedance to ejection across the aortic valve increases. The left ventricle adapts to this mechanical load by myocardial hypertrophy, increasing both wall thickness and left ventricular mass.[7] The wall stress (tension per unit of cross-sectional area) remains relatively normal because the compensatory increase in wall thickness parallels the increase in systolic pressure.[8,9] Only in the late stages of aortic stenosis does myocardial function deteriorate, with an increase in end-diastolic volume and a decrease in stroke volume, cardiac output and ejection fraction.

The adaptations and responses of the myocardium to a chronic pressure overload have been studied extensively in experimental animals. Initial work by Spann and co-workers,[10] using cat papillary muscle taken from hypertrophied right ventricle, showed that hypertrophy alone leads to a depression of the myocardial contractile state when measured by the maximal velocity of contractile element shortening (V max). However, more recent studies with the same preparation have suggested that the contractile state returns to normal when assessed after a more prolonged

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adaptation to the pressure load.[11] The time dependence of this adaptive process has also been shown in the whole heart of conscious dogs.[12] When a pressure load was acutely imposed by the inflation of a cuff surrounding the ascending aorta and sustained for an average duration of 19 days, the left ventricle responded initially by utilization of the Frank-Starling mechanism with an increase in both end-diastolic volume and pressure. This response was inadequate to meet the demands caused by the pronounced increase in wall stress, and myocardial shortening, as measured by the mean velocity of circumferential fiber shortening (Vcf), deteriorated acutely. Over the next several weeks, progressive hypertrophy and increase in wall thickness resulted in a decline of wall stress toward normal, with the eventual restoration of mean Vcf and end-diastolic volume to normal.[12] Therefore, in the canine heart the extent and velocity of left ventricular shortening declines in response to an acutely imposed pressure load, but with a relative return to normal of myocardial wall stress by hypertrophy, chamber shortening returns to normal levels.[13] These observations would suggest no major intrinsic change in contractile state attendant to the process of hypertrophy in experimental aortic stenosis.

In human subjects with valvular aortic stenosis, the adaptive process of hypertrophy spans a much longer time period under much less controlled conditions; consequently, the evaluation of myocardial pathophysiology is much more difficult and incomplete. Recently we analyzed the characteristics of left ventricular contraction during ejection in 15 subjects with valvular aortic stenosis using frame-by-frame measurements of ventricular dimensions and high-quality left ventricular pressure recordings registered either simultaneously with the left ventriculogram or nonsimultaneously but at an equivalent heart rate. In five of these subjects (open circles, Figure 3) peak dP/dt, ejection fraction, and mean wall stress were clearly normal, indicating maintenance of normal ventricular and myocardial function. In five other subjects (closed circles), peak dP/dt was normal while ejection fraction was low normal and mean wall stress was elevated; in this group the extent of shortening was adequately maintained in the face of increased afterload. However, in five further subjects (closed triangles) with increased mean wall stress, both peak dP/dt and ejection fraction were depressed. Since isovolumic peak dP/dt is measured before ejection

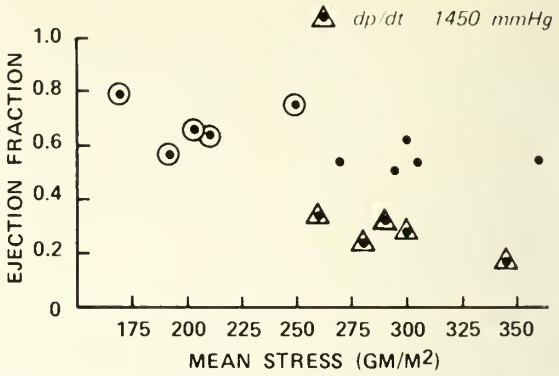

Figure 3.—Myocardial function measured by ejection fraction related to mean left ventricular wall stress in patients with aortic stenosis. Patients (triangles) with decreased ejection fraction also had decreased peak dP/dt, suggesting myocardial dysfunction (see text).

and before the ventricle "sees" the aortic valve obstruction, the low values (less than 1,450 mm of mercury per second) observed in this latter group suggest that depression of myocardial contractile state, as well as a relatively high mean wall stress, contributes to compromise of left ventricular function in some patients with aortic stenosis. Further studies are needed to clarify the likelihood of abnormalities in left ventricular function returning to normal after aortic valve replacement in the latter two subsets of patients.

Another consequence of myocardial hypertrophy is an increase in both mean left atrial pressure and left ventricular end-diastolic pressure, presumably secondary to increased stiffness of the left ventricular chamber during diastole as a consequence of increased wall thickness.[14] One of the intriguing questions concerning aortic stenosis is whether the accompanying hypertrophy leads to intrinsic changes in stiffness of the individual myocardial fibers or, alternatively, whether the increased chamber diastolic stiffness results solely from an increased wall thickness. Recently we analyzed this question using simultaneous measurements of left ventricular pressure and volume to obtain the myocardial stress-strain relationship in normal subjects and in symptomatic patients with advanced myocardial hypertrophy secondary to valvular aortic stenosis. Using these measurements, it was found that the intrinsic stiffness of the myocardium was not significantly different between the two groups. Therefore, it might be predicted that elevated filling pressures and abnormal diastolic properties of the left ventricular chamber would not persist permanently if hypertrophy regresses following aortic valve replacement in most patients.

Aortic regurgitation imposes a volume overload on the left ventricle. Adaptation to this load occurs by an increase in chamber size such that the total stroke volume increases in proportion to the regurgitant volume while the forward stroke volume and cardiac output remain normal. In spite of left ventricular enlargement, the wall stress can remain normal due to myocardial hypertrophy and to geometric alterations by which the ventricle assumes a more spherical shape.[8,9] Myocardial function is usually well preserved until the late stages of chronic aortic regurgitation.

The left ventricle responds to a volume overload initially by near-maximal use of the Frank-Starling mechanism. The ability to increase the total stroke volume by this mechanism alone, however, is limited. Ultrastructural studies of acutely overdistended canine left ventricles show that the midwall sarcomere lengths average 2.25μ, a magnitude which is near the apex of the sarcomere length-tension curve.[15] Further distention of the sarcomere down the descending limb of the Frank-Starling curve is resisted even at very high filling pressures. This maximal use of "preload reserve" in the acute volume-distended ventricle is not associated with a significant change in mean Vcf or other ejection phase indices.[16] Therefore, the left ventricle appears to adapt more readily to acute volume rather than to acute pressure overload.

As the volume overload persists, the left ventricular end-diastolic volume progressively increases. This increase in volume requires adaptations other than the Frank-Starling phenomenon. Again, ultrastructural studies from chronically volume overload dog hearts have shown that midwall sarcomere lengths averaged 2.19μ, not significantly different from acutely distended dog hearts.[17] Consequently, the major adaptation of the left ventricle to chronic volume overload involves the addition of new sarcomeres in series, allowing the ventricle to increase its end-diastolic volume dramatically without an accompanying change in end-diastolic pressure. The ejection phase indices (normalized per unit length) generally remain normal even with greatly dilated hearts.[18] For example, in dogs with volume overloads induced by a large aortocaval fistula, the maximum velocity of shortening (V max) measured from the force-velocity curve remained normal even when pronounced peripheral edema, ascites and pleural effusion developed in these dogs.[19] However, it is well known that in humans with chronic aortic regurgitation, myocardial function eventually and insidiously deteriorates. The structural or biochemical changes that lead to irreversible depression of the contractile state in chronic volume overloading remain unknown.

It is to be hoped that further laboratory investigation will define these changes and allow their earlier clinical detection[20] so that earlier surgical intervention can prevent irreversible damage.

DR. JOHNSON: *As Drs. Tsuji and Peterson have discussed, the pathophysiology and adaptations to the increased pressure burden imposed by aortic stenosis, and the volume overload associated with aortic regurgitation, are distinctly different, and are responsible for different natural histories and different clinical presentations in these two disorders. Dr. Robert Engler will now discuss the clinical features of aortic valve disease in the context of our knowledge of the pathophysiology of aortic valve disease.*

Historical and Physical Findings in Patients with Aortic Valve Disease

ROBERT L. ENGLER, MD*

PATIENTS WITH AORTIC STENOSIS commonly come to medical attention because of the detection of a heart murmur in the absence of associated symptoms, or they may present with one or more of the classical symptoms associated with aortic stenosis: congestive heart failure, ischemic chest pain, or syncopal/semisyncopal episodes.[21] In a patient with suspected hemodynamically significant aortic stenosis, meticulous attention should be paid to the details of each of these symptom complexes.

Initial presentation with congestive heart failure is uncommon in a patient with aortic stenosis who has neither a history of heart murmur nor previous symptoms. Usually a history of insidious and rather subtle progression of fatigue and dyspnea for the preceding months or years will be elicited, associated with gradual curtailment of activities almost unnoticed by the patient. However, a patient may suddenly develop symptoms of con-

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gestive failure if an added hemodynamic burden or insult occurs—loss of sinus rhythm, thyrotoxicosis, anemia, ischemia secondary to coronary artery disease, febrile state or the like. In the absence of these precipitating causes, signs and symptoms of overt congestive heart failure usually indicate that the patient is in the very late stages of the natural history of aortic stenosis and probably significant myocardial disease has developed.

The second major symptom associated with aortic stenosis is angina pectoris. In a significant proportion of cases, angina pectoris occurs in the absence of coronary artery disease and is secondary to the increase in myocardial oxygen demands imposed by increased left ventricular mass, associated with probable changes in subendocardial blood supply occurring in the setting of increased wall thickness, increased end-diastolic pressure and increased wall tension.[22] However, many patients with aortic stenosis, particularly those beyond the fifth decade, have angina pectoris in association with significant arteriosclerotic coronary artery disease.[23] In these patients it may be quite difficult to determine which is the dominant factor responsible for angina pectoris, and cardiac catheterization and coronary angiography may be indicated.

The third dominant symptom in aortic stenosis is that of syncope or presyncopal episodes. Syncope due to aortic stenosis is usually exertional or postexertional. Current evidence suggests that the mechanism of syncope in aortic stenosis is a lack of appropriate reflex vasoconstriction in nonexercising muscles[24] or in some patients acute left ventricular failure,[25] both of which may result in hypotension. This reflex activity may be due to inappropriate left ventricular baroreceptor responses to elevated left ventricular systolic pressure despite peripheral hypotension. Syncopal episodes are uncommon in the absence of either angina or some degree of congestive heart failure;[4] therefore, when an occasional patient presents with syncope as an isolated symptom in the setting of suspected significant aortic stenosis, the various cardiac and noncardiac causes for syncope must be diligently explored. Syncope may be caused by intermittent heart block due to extension of calcium from the aortic valves to the region of the atrioventricular junction in the adjacent interventricular septum, or by tachyarrhythmias, particularly those associated with the loss of atrial systole. If no other cause of syncope can be determined, the physician is obligated to seek supportive evidence that significant aortic valvular obstruction exists.

On physical examination in patients with aortic stenosis, a narrow peripheral arterial pulse pressure and a slow rising carotid pulse commonly are noted, but it should be kept in mind that the pulse pressure and pulse contour can be modified by arteriosclerosis, hypertension, or associated aortic regurgitation. For this reason, one gains the most information with respect to pulse volume and pulse contour by examination of the carotid pulse, which is least influenced by these factors. The jugular venous pulse may have a prominent A-wave due to hypertrophy of the interventricular septum, or may be normal unless right heart failure accompanies the late stages of aortic stenosis. On examination of the precordium in the typical case, an apical impulse is found that is not displaced but is sustained and diffuse, and usually there is a palpable presytolic impulse. If the cardiac apex is displaced, coexistent left ventricular myocardial disease, associated aortic regurgitation, or mitral regurgitation should be suspected. While a systolic thrill may be felt either at the apex or the base, particularly with the patient standing or sitting with the breath held in exhalation, the presence of a thrill does not necessarily imply severe valvular aortic stenosis and can be felt in patients with trivial aortic stenosis who have either a thin chest wall or a large stroke volume.[26] The important feature of the auscultatory examination is the character of the systolic ejection murmur, which in significant aortic stenosis persists through most of systole and peaks in the latter half of systole (Figure 4). If the aortic valve is rigid and immobile, the aortic second sound may be absent. With the prolongation of left ventricular ejection in aortic stenosis, there may be paradoxical splitting of the second heart sound. Commonly, an ejection sound accompanies aortic stenosis secondary to a mobile but congenitally abnormal valve; however, this finding is not a reliable indicator of the degree of obstruction. The presence of a fourth heart sound (S_4) in patients under age 40 implies significant aortic stenosis. The absence of a fourth heart sound in patients over the age of 40 would suggest that aortic stenosis and left ventricular hypertrophy are not severe; however, 15 percent of patients with critical aortic stenosis may lack an S_4.[27,28] An S_3 gallop, particularly in older patients, is very suggestive of associated myocardial disease or congestive heart failure.

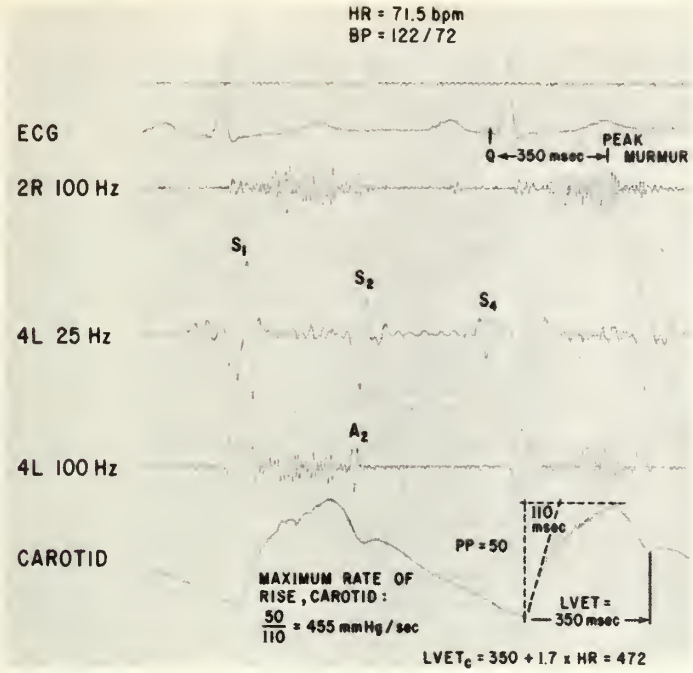

Figure 4.—Electrocardiogram (ECG), phonocardiogram and carotid pulse tracing from a patient with aortic stenosis. LVET = left ventricular ejection time; LVETc = rate and sex corrected LVET. PP = pulse pressure obtained with a sphygmomanometer, in this case 122 − 72 = 50 mmHg; A2 = aortic closure sound; S1 = first heart sound; S4 = atrial diastolic gallop; 2R = second right intercostal space; 4L = fourth left intercostal space; HR = heart rate. BP = blood pressure.

Carotid upstroke time from onset of systolic rise in carotid pulse to peak **(horizontal dashed line)** is 250 msec, normal <120 msec.

The peak of the systolic murmur recorded at the second right interspace (2R) is 350 msec after the Q wave of the ECG; a murmur peaking more than 250 msec after the Q wave suggests significant aortic stenosis.

Examination of an elderly patient who is suspected of having aortic stenosis can be quite challenging. The expected slow upstroke of the carotid pulse and small pulse pressure present in significant aortic stenosis may be normalized by an arteriosclerotic peripheral arterial tree or by hypertension. Left ventricular hypertrophy, usually appreciated by palpation of the cardiac apex, may be masked by emphysema or an increased anteroposterior chest diameter. Likewise, the systolic murmur may be faint and best heard at the cardiac apex due to changes in the chest wall configuration accompanying age.[2] Therefore, one must pay careful attention to all of the features of the cardiac examination, and maintain a high index of suspicion that significant aortic stenosis exists. With such a patient, one commonly must proceed to noninvasive and occasionally invasive diagnostic studies to determine the presence or absence of significant aortic stenosis.

Another important and not uncommon clinical situation is a patient who initially presents with severe congestive heart failure and low cardiac output; in such a case, one might find a very unimpressive murmur in the setting of severe aortic stenosis. In *any* patient with congestive heart failure, a systolic murmur deserves careful examination and periodic reevaluation after therapy to assess whether or not treatment of the congestive heart failure has resulted in an improvement in cardiac performance and more reliable physical findings.

In chronic aortic regurgitation, left ventricular dilatation and changes in left ventricular mass and shape frequently maintain cardiac output and left ventricular function so that patients remain asymptomatic despite significant quantities of regurgitation. Mild dyspnea on exertion, fatigue and excessive sweating may be symptoms of moderate or severe disease. Angina pectoris tends to occur late in the course and may be "atypical" (it is more frequent at night, while patients are supine).[29]

In patients with acute severe aortic regurgitation the symptoms provide a sharp contrast to the minimal symptoms of chronic, compensated aortic regurgitation; the left ventricle quickly exhausts its preload reserve (ability to dilate in response to the volume load) and, in the absence of hypertrophy, a sudden elevation in end-diastolic pressure leads to symptoms of pulmonary venous congestion (dyspnea) and sympathetic discharge (tachycardia and diaphoresis). The progression of symptoms to pronounced dyspnea at rest may take only a few days, or it may occur over several weeks or months.

The causes of acute aortic regurgitation include bacterial endocarditis, aortic dissection, ruptured aortic cusp (due to Marfan syndrome or myxomatous valve degeneration), trauma or sinus of Valsalva aneurysm. Chronic aortic regurgitation can be due to any of these, as well as to rheumatic heart disease, congenital malformations, syphilis, certain rheumatic diseases (ankylosing spondylitis), hypertensive dilatation of the aortic

root and aortitis. Therefore, in evaluating a case of aortic regurgitation, the physician must pay appropriate attention to the historical and physical clues to the many possible underlying causes.

The systemic blood pressure in aortic regurgitation is determined to a large extent by the state of the peripheral vessels; consequently, the pulse pressure (systolic-diastolic) in aortic regurgitation may vary widely as a function of peripheral vascular resistance and heart rate. In determining the diastolic pressure, care must be taken to note the point at which the Korotkoff sounds become muffled—pistol shot sounds may continue down to zero, but the true diastolic pressure is rarely less than 40 mm of mercury. Hill sign, a pulse pressure measured in the leg which exceeds that in the arm by 40 mm of mercury, is generally accepted to imply severe aortic regurgitation (despite lack of careful hemodynamic substantiation). The increased stroke volume accompanying significant aortic regurgitation produces a carotid pulse with a rapid upstroke and diastolic collapse which may be bisferiens, as well as other signs accompanying a wide pulse pressure which include pistol shot sounds over peripheral arteries, Durozier's to-and-fro bruit (produced by light stethoscope pressure over the femoral artery) and visible capillary pulsations in the nail beds.

The cardiac apical impulse is almost always displaced, enlarged and sustained in chronic severe regurgitation. The high pitched diastolic decrescendo murmur of aortic regurgitation is heard best at the aortic area or apex with the patient upright and the breath held in expiration. Aortic regurgitation due to aortic root dilatation is often louder on the right of the sternum in the fourth intercostal space, while that due to valvular disease is best heard on the left side. Cooing or musical diastolic murmurs suggest eversion of an aortic cusp vibrating in the regurgitant stream. In chronic aortic regurgitation, moderate severity is usually accompanied by a nearly holodiastolic murmur; however, exceptions are frequent enough to make this sign unreliable. The systolic flow murmur present with moderate or severe aortic regurgitation is short and occurs early in systole.

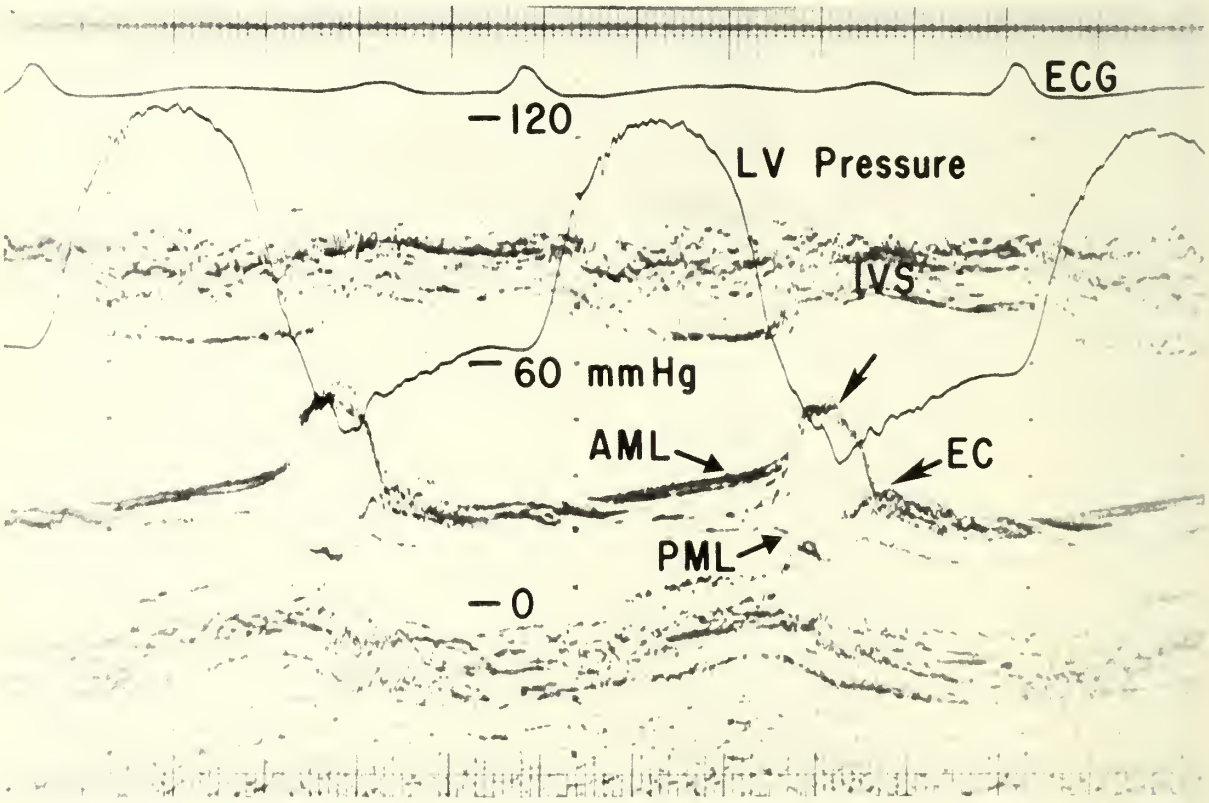

Figure 5.—Echocardiogram of the mitral valve and simultaneous left ventricular pressure in a patient with acute aortic insufficiency due to endocarditis. AML = anterior mitral leaflet; PML = posterior mitral leaflet; IVS = interventricular septum. Diastolic fluttering of the AML is present **(unlabeled arrow).** Early closure (EC) of the mitral valve is apparent with notably elevated left ventricular diastolic pressure; aortic regurgitation continues but filling across the mitral valve occurs only early in diastole.

Longer, late peaking systolic murmurs suggest concomitant aortic stenosis. The Austin Flint murmur is a low frequency diastolic rumble, often with presystolic accentuation, heard at the left ventricular apex with the patient in the left lateral decubitus position using light pressure on the bell of the stethoscope. This murmur is presumably generated by the anterior mitral leaflet being "pushed" toward its closed position into the path of antegrade mitral flow by the aortic regurgitant stream; earlier onset and longer Austin-Flint rumbles correlate with more severe aortic regurgitation.[30,31] Differentiation of this murmur from anatomic mitral stenosis is important; a true mitral stenosis rumble will increase after inhalation of amyl nitrite or exercise, due to increased mitral flow, whereas the Austin Flint rumble will diminish after amyl nitrite inhalation as aortic regurgitation becomes less. An S_3 or ventricular diastolic gallop is usually present in moderate aortic regurgitation; its presence does not imply left ventricular failure. An S_4 gallop in younger patients is an important clinical sign and suggests latent left ventricular dysfunction.

An important problem in chronic aortic regurgitation is the recognition of associated hypertensive disease. Clues to significant hypertension include diastolic blood pressures greater than 80 mm of mercury, systolic pressures greater than 160 mm of mercury and left ventricular hypertrophy out of proportion to the severity of aortic regurgitation. Since diastolic hypertension increases the volume of regurgitation, its treatment takes on special importance.

The physical signs in acute aortic regurgitation, in contrast to those in chronic aortic regurgitation, are characterized by the early onset of congestive heart failure, pulmonary edema and right ventricular failure. The pulse pressure may not be notably wide and the diastolic murmur may be short and soft, at least in part due to the pronounced elevation in left ventricular diastolic pressure. This may lead to early closure of the mitral valve (Figure 5), with an associated sound in mid-diastole, and a soft or absent S_1 regardless of the PR interval.[32] Tachycardia and an S_3 gallop are almost always present. Severe congestive heart failure can develop with great rapidity in acute aortic regurgitation and carries a very poor prognosis without surgical intervention.

DR. JOHNSON: *Not uncommonly in patients with aortic valve disease, the history and physical examination leave significant questions about the severity of the underlying hemodynamic derangements. Dr. Martin LeWinter will discuss the value and use of various noninvasive diagnostic methods available to help solve these problems.*

Use of Noninvasive Diagnostic Methods in Aortic Valve Disease

MARTIN LeWINTER, MD*

HELPFUL INFORMATION regarding diagnosis and management of patients with aortic valve disease can be gained from the use of various noninvasive methods, particularly systolic time intervals and echocardiography.

Systolic Time Intervals

Because valvular aortic stenosis so directly and distinctively affects the systemic arterial pulse, the use of indices derived from the indirect recording of the arterial pulse is one of the most helpful noninvasive laboratory studies that can be done in evaluating an aortic outflow murmur. Indirect pulse wave recording from the carotid artery in the neck is a technically simple and reproducible method for calculation of these indices. The carotid pulse, electrocardiogram and phonocardiogram are recorded (Figure 4) at rapid paper speed and ten cardiac cycles are averaged at mid-expiration. The onset of the carotid upstroke is obtained by visual inspection, and the end of ejection is taken at the trough of the dicrotic notch. Several indices derived from these measurements correlate with significant valvular aortic stenosis; among these are the maximum rate of rise of arterial pulse (lower limit of normal 500 mm of mercury per second),[33] the left ventricular ejection time (LVET), the carotid upstroke time and the Q-peak murmur time. The LVET corrected for heart rate and sex using appropriate regression equations (LVET index) has been shown to be both a sensitive and specific test for the detection of significant aortic stenosis; these studies indicate that if the LVET index exceeds 420 msec, significant aortic stenosis (a gradient of more than

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50 mm of mercury) is likely.[33,34] Several factors may be responsible for a misleading LVET index in the presence of significant aortic stenosis: (1) Severe left ventricular dysfunction independently shortens the ejection time if the stroke volume is reduced; the clinical features usually will suggest whether or not this is the case. (2) The presence of other valvular lesions in addition to aortic stenosis may also affect the LVET. Thus, coexistent aortic regurgitation may prolong the ejection time. Mitral stenosis may shorten the ejection time if the stroke volume is reduced. Once again, these factors will generally be apparent and can be taken into account when the ejection time is interpreted. (3) Digitalis therapy will shorten ejection time in the presence of significant aortic stenosis, as in other disorders. The presence of localized carotid disease proximal to the recording site may distort the carotid pulse contour, causing in particular an apparently slow upstroke, but carotid disease usually does not affect the total measured ejection time; consequently the LVET index retains its utility if the dicrotic notch can be identified.

In contrast to aortic stenosis, the LVET in aortic regurgitation is *not* a reliable guide to the severity of aortic regurgitation. In patients with mixed aortic stenosis and regurgitation the LVET index is not useful if it is prolonged, but a *normal* LVET generally rules out significant obstruction, provided none of the previously mentioned factors which might independently shorten or lengthen the LVET are present.

Echocardiography

Echocardiography in general provides supportive but not definitive information with respect to the presence of significant aortic valve obstruction. Ultrasonic examination of the aortic valve leaflets themselves may yield information in several ways. First, the leaflets may be seen to be abnormally thickened, providing direct evidence of diseased leaflets, but not necessarily of significant outflow obstruction. At the same time, during systole the leaflets may show less excursion toward the aortic wall than normal (Figure 6). This finding, however, may also be observed in low cardiac output states in the absence of aortic valve disease. The echocardiogram may also be used to derive information with regard to left ventricular velocity of circumferential fiber shortening (Vcf) and wall thickness in the patient with aortic stenosis, both of which may be helpful in assessing the degree of hypertrophy and the status of left ventricular function in such patients.[35] Therefore, it may be possible to detect abnormalities in left ventricular function which are not apparent using other noninvasive techniques (Figure 7). Another abnormal echocardiographic finding which may be noted in aortic stenosis is reduction of the E-F slope of the anterior mitral valve leaflet. This finding has generally been considered to reflect reduced left ventricular compliance, and is not specific for aortic stenosis.

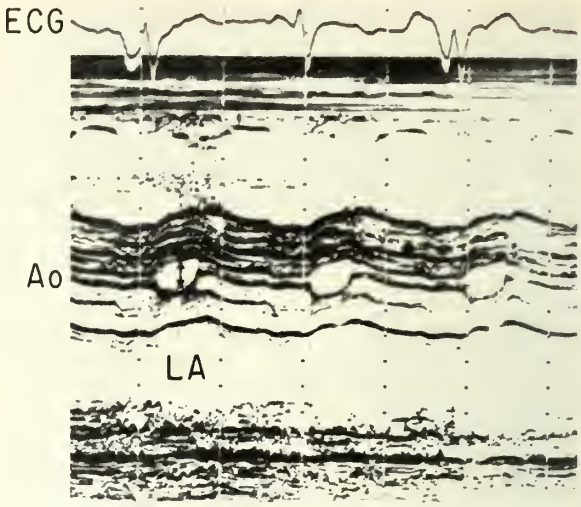

Figure 6.—Echocardiogram of aortic root, aortic valve and left atrium in a patient with aortic stenosis. Arrow indicates decreased opening of the aortic valve (normal >1.6 cm). Dense echoes surrounding the valve opening suggest valve calcification. ECG = electrocardiogram; A_o = aorta; LA = left atrium.

Perhaps the most specific echocardiographic finding in aortic regurgitation is diastolic oscillation or fluttering of the anterior mitral valve leaflet, shown in Figure 5. While this finding does not appear to occur in trivial aortic regurgitation, it does not correlate with the magnitude of the regurgitant leak or the presence of an Austin-Flint rumble.[36] As discussed by Dr. Engler, the Austin-Flint rumble sometimes heard in aortic regurgitation can be confused with the rumble of mitral stenosis; echocardiographic recording of mitral leaflet motion is useful in making the distinction between the two.

A valuable finding in acute, severe aortic regurgitation is that of early closure of the mitral valve, illustrated in Figure 5. Because the murmur of aortic regurgitation may be deceptively short and the pulse pressure may not be notably wide, it is extremely helpful to have this reliable noninvasive finding on which to base the diagnosis

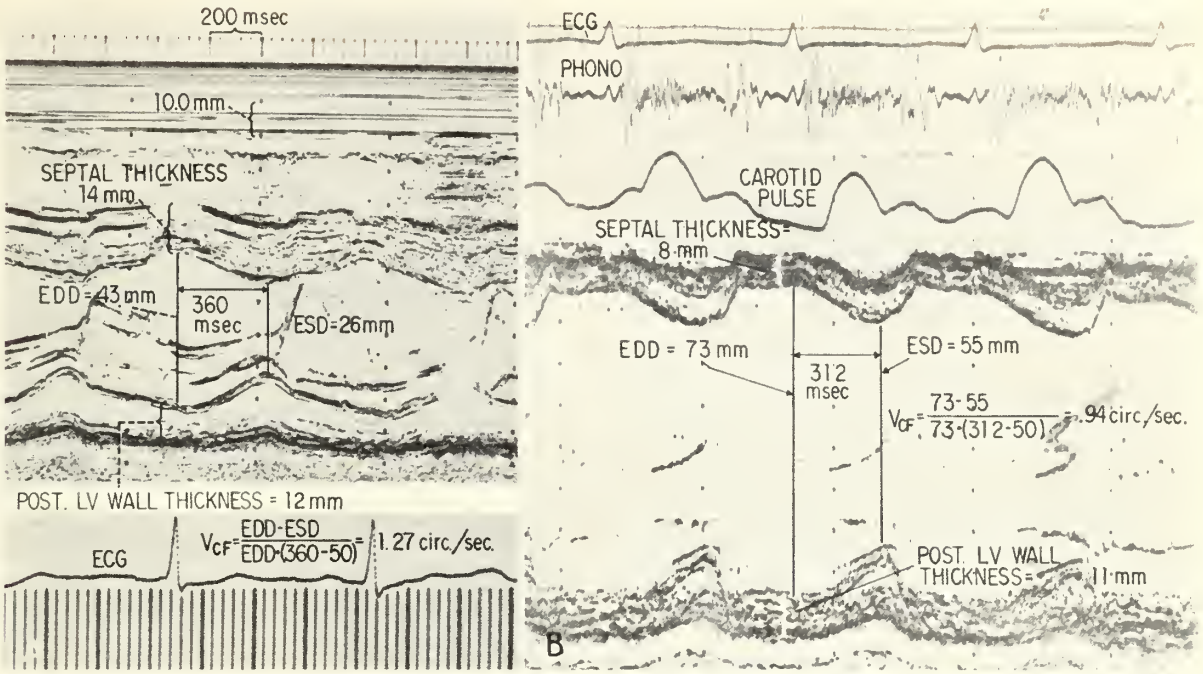

Figure 7.—Measurement of left ventricular wall thickness and velocity of circumferential fiber shortening (Vcf) in two patients with aortic stenosis. **A,** a patient with normal Vcf and increased wall thickness. **B,** a patient with left ventricular dilatation, normal wall thickness and decreased Vcf. The method for calculation of Vcf is shown. EDD = end diastolic diameter, measured at the apex of the R wave of the ECG; ESD = end systolic diameter. Left ventricular ejection time is taken as the distance between these two events minus 50 msec.

of acute, severe aortic regurgitation. Early mitral valve closure presumably results from the extremely high left ventricular diastolic pressure.[32,37]

As with aortic stenosis, appreciation of the presence of leaflet disease may be gained if the aortic leaflets appear thickened. On the other hand, if aortic root dilatation rather than valve disease is the cause of the regurgitation, an abnormally large aortic root diameter may be apparent on echocardiography while the leaflets themselves appear normal. As in aortic stenosis, echocardiography can be applied in aortic regurgitation for analysis of left ventricular function. Measurements of shortening of a single chord across the minor axis of the ventricle should in theory be representative of the ventricle as a whole. However, with aortic regurgitation, this may not be the case. The response of the normal left ventricle to volume overload is dilatation and, in the process, changes in its shape occur. Additionally, the presence of segmental shortening abnormalities in chronic aortic regurgitation have been noted.[38] Because of these factors, the echocardiogram may not accurately reflect global left ventricular function in a patient with aortic regurgitation. In this regard, Johnson and co-workers have recently documented that echocardiographic indices of left ventricular function may overestimate global left ventricular performance when compared with biplane angiographic indices.[39] Therefore, significantly abnormal left ventricular function may not be detected using the ultrasound technique. While these considerations do not necessarily invalidate the ability of echocardiography to detect abnormal left ventricular function in aortic regurgitation, particularly when an individual patient is studied serially and used as his own control, they do indicate the need for further critical examination in this area.

Dr. Johnson: *As has been discussed, aortic stenosis and aortic regurgitation are accompanied typically by a long natural history during which important changes in hemodynamic and myocardial function occur. A physician caring for such patients must be alert to these factors in outlining a plan of medical management. Dr. Joel Karliner will continue this conference with a discussion of the medical management of patients with aortic valve disease.*

Medical Management of Aortic Valve Disease

JOEL KARLINER, MD*

IN GENERAL, all patients with aortic valve disease should be counseled regarding the necessity of paying particular attention to the state of their general health, and should be apprised of the symptoms of endocarditis and the necessity for, and details of, endocarditis prophylaxis. In patients with aortic stenosis who are without the typical symptoms of angina pectoris, syncope or congestive cardiac failure, intelligent observation and *careful* follow-up are generally all that are required. Patients must be cautioned to report any symptoms to the physician, and yearly or more frequent x-ray studies of the chest, electrocardiograms and determinations of systolic time intervals are indicated to assess the progression of aortic stenosis and left ventricular hypertrophy. Asymptomatic patients with suspected significant aortic stenosis should be cautioned to avoid exercise which is strenuous or excessive, including jogging and competitive sports. Such limitation of vigorous activity need not apply to a person with mild to moderate disease. Although treadmill or bicycle exercise testing may be helpful in defining symptoms more accurately in individual patients, particularly those who are asymptomatic but with suspected significant stenosis, such procedures are potentially dangerous and should be carried out with caution. If doubt persists as to the severity of the lesion, cardiac catheterization is indicated.

Whether or not digitalis glycosides should be prescribed for patients with left ventricular hypertrophy of any cause is uncertain. As discussed by Drs. Peterson and Tsuji, while some evidence indicates that the process of hypertrophy in aortic stenosis may be associated with depression of left ventricular performance, recent experimental work indicates that this is probably not the case, at least during the early stages of left ventricular hypertrophy.[12] There is no evidence in humans that digitalis therapy in this setting can delay the progression of left ventricular hypertrophy. In patients with significant aortic stenosis it is uncommon for electrocardiographic findings to be normal[4,40] and administration of digitalis may induce repolarization changes in electrocardiograms which might complicate the diagnosis of left ventricular subendocardial ischemia and hypertrophy. Therefore, on balance, digitalis glycosides probably should not be used prophylactically in patients with aortic stenosis and left ventricular hypertrophy unless congestive cardiac failure is present, or reduced left ventricular performance can be demonstrated by noninvasive methods.

Diuretics should be employed in the treatment of congestive cardiac failure, but with appropriate caution, since vigorous diuresis may lead to orthostatic hypotension and fatal arrhythmias.[29] Such an occurrence may be expected in patients with aortic stenosis because in such patients the use of the Frank-Starling mechanism is required and often an elevated left ventricular end-diastolic pressure to achieve an adequate cardiac output is needed. When end-diastolic volume is reduced beyond a critical level by diuretic medication, the cardiac output may decline, resulting in inadequate coronary or cerebral perfusion, or both. In this situation, however, strong consideration should be given to cardiac catheterization and aortic valve replacement.

Other conventionally employed drugs should also be used with caution. For example, propranolol can depress myocardial function and induce left ventricular failure; it may reduce the heart rate response to exercise, leading to inadequate cardiac output and to decreased perfusion of vital organs. Furthermore, bradycardia is poorly tolerated in patients with aortic stenosis, as it causes the mean systolic gradient across the aortic valve to increase. Similarly, any antihypertensive agent (such as guanethidine) which depresses myocardial performance should not be used in patients with aortic stenosis.

Patients with chronic aortic regurgitation typically tolerate this lesion well and tend to be free of symptoms until relatively late in the course of disease, usually *after* the development of myocardial dysfunction.[5] Therefore, the goals of a physician in managing patients with aortic regurgitation are to: (1) prevent or postpone, if possible, the myocardial dysfunction that so insidiously complicates the course of chronic aortic regurgitation and (2) detect the earliest signs of myocardial dysfunction in an effort to properly time aortic valve replacement. Pertinent to these considerations, several important clinical questions remain unanswered. A question regarding the first of these goals is whether use of digitalis preparations early in the course of chronic, significant aortic regurgitation will decrease the amount of

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left ventricular dilatation, and thereby prevent or postpone the onset of myocardial disease. Our bias is toward use of digitalis preparations in a patient with left ventricular dilatation, as assessed by clinical, radiographic or echocardiographic techniques, before the onset of either overt depression of systolic ventricular performance or of significant symptoms of heart failure. Certainly, once symptoms of circulatory congestion appear, aggressive therapy with digitalis glycosides, diuretics and sodium restriction is indicated. Again, considering the goal of preventing myocardial dysfunction, systemic arterial hypertension is a particular problem in a patient with aortic regurgitation, because it increases regurgitant volume and systolic wall stress, and the natural history of aortic regurgitation might thereby be accelerated. Therefore, as discussed by Dr. Engler, significant hypertension should be appropriately treated. However, the use of drugs that might decrease the inotropic state of the ventricle or result in bradycardia—such as propranolol, reserpine or guanethedine—should be avoided.

Atrial fibrillation, while uncommon in isolated aortic regurgitation, may be poorly tolerated if atrial systole is an important contributor to end-diastolic volume in a given patient, and cardioversion may be required. Bradyarrhythmias may also be detrimental and may require the use of a permanent pacemaker to reverse the increase in left ventricular volume and pressure caused by long diastolic periods.[4]

Exercise, in general, is well tolerated, as it is accompanied by an increase in heart rate, and a decrease in aortic impedance, both of which reduce the volume of aortic regurgitation.[42] However, any situation which provokes symptoms should be closely evaluated and avoided if it appears to be causing an excessive hemodynamic burden.

Indications for and Objectives of Cardiac Catheterization in Aortic Valve Disease

ALLEN D. JOHNSON, MD

THE TIMING of cardiac catheterization in aortic stenosis, in general, is related to our knowledge of the natural history of this disorder. Once angina, congestive heart failure or otherwise unexplained syncope occurs in a patient with significant aortic stenosis, life expectancy is significantly abbreviated in the absence of surgical relief of the valvular obstruction.[4,21] When any one of these symptoms is present, cardiac catheterization, in anticipation of aortic valve replacement, is indicated. When doubt exists regarding the severity and relative contribution of aortic valve disease in a patient with angina, suspected coronary artery disease, calcium in the region of the aortic valve and a systolic ejection murmur (not an uncommon clinical situation), cardiac catheterization is often necessary to establish the presence and severity of aortic stenosis, and to plan appropriate surgical or medical therapy. More controversial is the decision regarding cardiac catheterization in an asymptomatic patient with suspected severe aortic stenosis. Approximately 5 percent of such patients beyond adolescence will die suddenly without symptoms.[21] However, since operative mortality is in the same range, we prefer to postpone catheterization and surgical therapy until symptoms are present.

The goals of cardiac catheterization in aortic stenosis are:

- *To document the severity of the aortic obstruction.* This requires accurate measurement of the cardiac output simultaneously with measurement of the left ventricular and systemic arterial (preferably ascending aortic) pressures. The aortic valve can usually be crossed retrogradely from the brachial or femoral approach; however, transseptal catheterization of the left ventricle is occasionally required and is particularly useful in such a case. Using the Gorlin formula (aortic valve area = systolic flow/K $\times \sqrt{\text{gradient}}$), the approximate aortic valve area can then be calculated, assuming there is insignificant aortic regurgitation. Careful attention should be directed to the interpretation of the peak and mean systolic aortic valve pressure gradients, as the gradient will vary directly with the square of the systolic blood flow across the valve per unit time, and a low cardiac output could be associated with a low

gradient in the setting of a severely stenotic aortic valve. While "significant" aortic stenosis has been arbitrarily judged to be present if the peak gradient is greater than 50 mm of mercury, and if the aortic valve area index is less than 0.7 sq cm per sq meter, these values should be considered approximate guidelines.[4,21] In a series of symptomatic, medically managed patients with catheterization documented "significant" aortic stenosis by these criteria, neither peak systolic gradient, calculated valve orifice area, cardiac index nor left ventricular end-diastolic pressure separated survivors from nonsurvivors.[4] In general, an aortic valve area less than 0.5 sq cm is considered to represent severe stenosis, and greater than 0.8 sq cm to represent mild stenosis.

• *To document the status of left ventricular function.* The left ventricular angiogram is evaluated qualitatively for wall motion, and quantitatively for ejection fraction, mean systolic ejection rate and Vcf. As Drs. Tsuji and Peterson have discussed, the increased left ventricular mass and wall thickness which accompany compensated aortic stenosis may not be associated with significantly abnormal function of the myocardium at the sarcomere level, and hypertrophy may well regress after relief of aortic obstruction.[12] However, it is well recognized that the late stages of aortic stenosis can be accompanied by severe left ventricular dysfunction with an increased end-diastolic volume and severely depressed ejection fraction. The natural history of unoperated, severe and symptomatic aortic stenosis is so dismal, however, that we exclude no patient from surgical therapy solely because of poor left ventricular function.

• *To document the location of left ventricular outflow obstruction.* While this specialty conference has been limited to valvular disease, it should be recognized that hypertrophic subaortic stenosis can coexist with valvular aortic stenosis,[43] and failure to recognize and document this situation could result in significant intraoperative and postoperative hemodynamic problems. It is important to search for concomitant hypertrophic subaortic stenosis in all cases of valvular aortic stenosis. Echocardiography can be helpful if systolic anterior motion of the anterior mitral leaflet is present. At cardiac catheterization, a positive Brockenbrough response (decrease in systemic arterial pulse pressure on a postpremature ventricular contraction beat), documentation of two levels of systolic pressure gradient (one below the aortic valve and one at the aortic valve) between the left ventricular inflow area and aorta, and high quality biplane left ventricular cineangiograms showing the typical features of anterior position of the anterior mitral leaflet during systole and septal prominence will provide evidence for the presence of hypertrophic obstructive cardiomyopathy.

• *To document the presence or absence of associated valve disease, particularly mitral regurgitation, mitral stenosis and aortic regurgitation.* Simultaneous measurement of pulmonary wedge or left atrial and left ventricular pressures should be done to search for and assess mitral stenosis; left ventriculography should be routinely carried out and will detect mitral regurgitation, and when the presence of significant aortic regurgitation is suspected a supra-aortic valve angiogram should be obtained.

• *To document the status of coronary circulation.* In patients with aortic stenosis beyond the age of 40, the presence or absence of angina pectoris does not accurately predict the presence or absence of coronary artery disease.[44] Since it appears that significant coronary artery disease does influence the operative results in aortic stenosis,[45,46] coronary artery bypass grafting may be warranted if significant coronary artery disease is present.

Aortic regurgitation presents a distinctly different set of problems to a clinical cardiac physiologist. As has been discussed, in chronic aortic regurgitation, myocardial dysfunction usually precedes significant clinical symptoms, and when established may be irreversible.[20] Therefore, if operative mortality and morbidity were negligible, and prosthetic valves infinitely durable and free from problems of thromboembolism, infection and hemolysis, aortic valve replacement could be timed to prevent the establishment of myocardial dysfunction. Further complicating the management of patients with aortic regurgitation is the lack of established clinical criteria, including noninvasive methods, for determining the presence of abnormal myocardial function. Our current approach to the timing of cardiac catheterization and valve replacement in patients with aortic regurgitation takes each of these factors into consideration. In all patients with symptoms of mild to moderate congestive left heart failure, in whom clinical and noninvasive data support the diagnosis of significant aortic regurgitation, catheterization studies are done. If significant depression of left

ventricular performance is present, surgical therapy is recommended even for class II (New York Heart Association) patients. In asymptomatic patients in whom there is evidence of progressive left ventricular enlargement on physical examination, chest x-ray or echocardiogram, or in whom electrocardiograms show increasing signs of left ventricular hypertrophy, or in patients in whom echocardiographic indices of left ventricular performance indicate a progression from normal to abnormal left ventricular systolic performance, cardiac catheterization is done. If left ventricular systolic function as assessed at catheterization is normal, careful medical management is recommended. The presence of significant depression of left ventricular performance warrants consideration for valve replacement. It is worth emphasizing that symptoms of congestive heart failure in patients with chronic aortic regurgitation are not as valuable in predicting survival following valve replacement as other measures of cardiac performance.[47]

A vexing problem encountered in patients with chronic aortic regurgitation is management of a patient who has significant aortic regurgitation and established, *severe* myocardial dysfunction. The natural history in this setting is poor, with progression of myocardial disease and limited longevity.[5,6] However, valve replacement in such cases does not appear to result in the reversal of myocardial dysfunction[20] and in preliminary studies the long-term results of surgical operation in this situation have not been encouraging.[48] In summary, one must decide between medical management with almost certain worsening of myocardial function, and the risk of surgical operation with the possibility of arrest without reversal of the deterioration of myocardial function, and no current evidence that the natural history will be positively affected. If symptoms are refractory to optimum medical management, valve replacement can be undertaken with the above mentioned expectations kept in mind.

At present, cardiac catheterization provides the most reliable means of assessing the function of the left ventricle in patients with aortic regurgitation; therefore, appropriate care and attention should be directed toward the assessment of left ventricular performance at the time of catheterization in these patients. Ideally, quantitative biplane ventriculography should be employed in patients with chronic aortic regurgitation. A recent study by Bolen and associates identified a group of patients with aortic regurgitation and normal basal left ventricular ejection fraction who responded to afterload stress (angiotensin) with a decrease in ejection fraction and left ventricular stroke work index. The authors felt that this response might indicate a state of latent left ventricular dysfunction.[49] Employment of a well-defined stress of this type might prove to be useful in the routine evaluation of left ventricular performance in aortic regurgitation.

Supravalve aortic root angiography is employed to roughly quantitate the degree of aortic regurgitation (trivial to 4+) and to document the anatomy of the aortic root, which may be quite dilated in Marfan syndrome or cystic medial necrosis. Coronary angiograms are routinely obtained in patients over age 40. Associated mitral valve disease—rheumatic and mitral prolapse in particular—should be evaluated with appropriate pressure recordings and analysis of the left ventricular cineangiogram.

Acute aortic regurgitation may overwhelm the usual compensatory mechanisms accompanying a volume overload, and left ventricular end-diastolic pressure may rise to produce severe pulmonary vascular congestion. If medical therapy, as outlined by Dr. Karliner, is not effective in relieving the congestive heart failure, cardiac catheterization followed by aortic valve replacement may be required, even in patients with active infective endocarditis. In patients with acute aortic regurgitation, therefore, the timing of cardiac catheterization and aortic valve replacement is dependent upon the severity of associated signs and symptoms of heart failure, in contrast to chronic aortic regurgitation.

Surgical Considerations in Aortic Valve Disease

PAT O. DAILY, MD*

As Dr. Johnson has discussed, the timing of aortic valve surgical therapy in a given patient requires synthesis and consideration of all the available clinical, noninvasive, angiographic and hemodynamic information. Presented with a patient in whom the decision for valve replacement has been made, a surgeon is faced with two prob-

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lems which at present do not have ideal solutions: (1) selection of a prosthetic replacement for the diseased aortic valve and (2) deciding upon a surgical technique which will provide the best operative results and the least chance of causing myocardial damage. Let us first consider selection of a prosthetic aortic valve.

Although many factors relate to selection of a valve substitute, the three primary considerations are hemodynamic performance, durability and the incidence of thromboembolism. Additional aspects such as availability and ease of insertion are important but are relatively equivalent for most of the currently used valve replacement devices. However, when aortic allografts were at the height of their popularity, procurement was a major obstacle in their use. It is, therefore, an evaluation of these three basic determinants that accounts for the selection of a particular valve replacement device for a specific patient.

Hemodynamic Considerations

Substitute valves can be basically divided into those having a central flow orifice and those with a lateral flow orifice. These designations relate to the fact that in central flow valves the direction of blood passage through the valve is not changed from the normal situation. Porcine xenografts and allografts are examples of central flow valves. In lateral flow valves, after passage through the primary orifice, blood flow is directed laterally upon striking the poppet. The various ball and disc valves are examples of lateral flow. Valves with a tilting disc such as the Bjork-Shiley and Lillehei-Kaster valves may be described as semicentral flow valves. Valves of this type have been reported to have very favorable hemodynamic characteristics, particularly in the smaller sizes.[50] From a hemodynamic standpoint alone, it appears that central flow type valves are more physiologically appropriate. However, a number of different prosthetic aortic valves appear to offer acceptable hemodynamic results.[52]

Durability

Most prosthetic valves have satisfactory durability, but problems have been encountered. In Braunwald-Cutter aortic prostheses cloth wear has been noted, as well as poppet embolization.[53] Cloth wear has also been a significant problem with the 2300 series Starr-Edwards valves. Allografts appear to have a poor record for durability; Karp and co-workers[54] found that in 10 to 15 percent of patients with aortic allografts reoperation was needed, despite a more enthusiastic early report.[55] Similar results were reported by Wallace and associates, with the probability of reoperation for valve failure being 7 percent within three years and 22 percent at five years in this series.[56] The method of allograft preparation is important; long-term results favor the fresh frozen[57] or fresh antibiotic preserved allografts.[58] Early experience with formalin preserved porcine xenografts resulted in a 50 percent failure rate at 42 months.[59] However, experience with gluteraldehyde fixed xenografts followed up to 46 months showed no valve failures.[60,62] The question of long-term durability in excess of four to five years of gluteraldehyde fixed porcine xenografts remains unanswered.

Thromboembolism

The primary argument for the use of allografts and xenografts is the very low incidence of thromboembolism without the necessity for anticoagulation. Aortic allografts seem virtually free of thromboembolism; several large series have reported no thromboembolic complications in the absence of atrial fibrillation.[62,63] With porcine xenografts there is an acceptably low incidence of thromboembolism without the use of anticoagulants.[59,60] Thromboembolism is significantly more frequent after aortic valve replacement with caged poppet or tilting disc prosthetic valve. The early Starr-Edwards Model 1000 prosthetic aortic valve was reported to have a thromboembolic incidence of 34 percent at three years.[63] Extension of fabric over the valve seat reduced the embolic rate to 5 percent at three years in the Starr-Edwards 1260 aortic valve. However, complete fabric enclosure of the metallic surfaces did not further reduce the thromboembolic rate in the 2300 series valves and resulted in the same thromboembolic rate as the Model 1260 valve. A recent comparison showed that the incidence of emboli at one year was 14.0 percent for the Braunwald-Cutter valve, 9.1 percent for the Starr-Edwards composite seat 2320 valve and 7.4 percent for the Starr-Edwards 1200 and 1260 silastic valves.[54] Anticoagulants were not used with the first two valves but were with the last. It therefore appears that complete covering of the entire valve cage has not achieved the goal of an acceptably low incidence of thromboembolism without anticoagulants. Accordingly, it is now recommended that anticoagulants be used with these valves.[54,65]

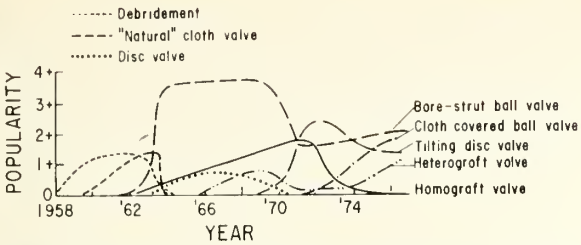

Figure 8.—Graphic estimate of popularity of aortic valve procedures. Adapted and modified with permission from McGoon.[66]

From the preceding discussion, it is apparent that no one valve is clearly superior in all respects to the others. This situation was very clearly portrayed as a graph in a recent editorial by McGoon.[66] With permission this graph has been updated and is presented in Figure 8. It is apparent that confusion exists, with the bare-strut ball valve, cloth covered ball valve, tilting-disc valve and xenograft enjoying nearly equal popularity. It is our preference to routinely use the Hancock porcine xenograft because of the very low incidence of thromboembolism without anticoagulants. While long-range durability of the xenograft is unknown, the current model has been associated with an extremely low incidence of failure over a 46 month period. In the case of smaller aortic roots, consideration is given to the Bjork-Shiley valve, with that valve being definitely preferred with aortic valve sizes of 21 mm and under.

Surgical Technique

The primary controversy regarding aortic valve replacement relates to the method of myocardial protection during the period of aortic cross clamping. Although a number of variations exist, the basic methods of myocardial protection are coronary perfusion by cannulation of the individual coronary arteries and myocardial hypothermia. Each method can produce clinically acceptable results. For example, McGoon[67] using coronary perfusion reported a series of 100 consecutive aortic valve replacements without mortality, and DeBoer and Midell[68] attributed continuous coronary perfusion as the single most important factor in achieving an operative mortality of 1.8 percent in 104 consecutive patients in whom aortic valve replacement was done. Myocardial surface cooling as described by Shumway and co-workers[69] has been used with equal success in several series of patients.[70-72] Our own experience is that myocardial surface cooling, although yielding an operative mortality of 1 percent in 100 consecutive patients in whom aortic, mitral and multiple valve replacement was done does not produce constant myocardial cooling.[73] Temperature gradients of as much as 20°C between the left ventricular epicardium and endocardium occur and persist. Furthermore, in a series of patients being evaluated after mitral valve replacement, a significant decrease in myocardial contractility was detected in several patients.[74]

With refinement of surgical methods, evaluation of the adequacy of surgical results and myocardial protection must primarily be concerned with chronic preservation of left ventricular function, rather than operative mortality.[75] As emphasized in a randomized study reported by Sapsford and associates,[76] it appears that either coronary perfusion or myocardial hypothermia can offer very acceptable clinical results. Unfortunately, there is evidence that neither method results in complete preservation of myocardial function. In a chronic experimental study, Brody and co-workers[77] found that coronary perfusion and myocardial surface cooling resulted in late depression of left ventricular function and produced myocardial fibrosis. Accordingly, refinements of existing techniques and other methods are being sought in an endeavor to enhance preservation of myocardial function. Because of the inconsistency of myocardial surface cooling mentioned above, our laboratory is presently involved in a comparison of myocardial surface cooling and cold cardioplegia (infusion of a cold electrolyte solution of high potassium content into the cross clamped aortic root and coronary arteries) as described recently by Roe and associates.[78]

Results of Aortic Valve Replacement

Although aortic valvuloplasty was extensively done in earlier years,[79,80] because of suboptimal long-term results, it has largely been replaced by aortic valve replacement. Consequently, this discussion will relate to valve replacement.

The essential aspects in considering the results of aortic valve replacement include operative mortality (30 days from operation), late mortality, symptomatic improvement and complications associated with valve replacement.

Current operative mortality is between 5 and 15 percent in most reported series and is less than 5 percent in selected reports. It is increasingly apparent that this mortality is determined more by patient selection than use of a particular pros-

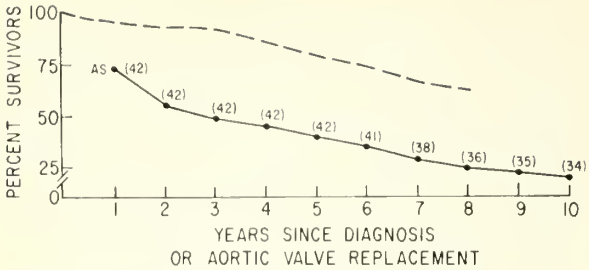

Figure 9.—Composite graph showing in the upper curve survival in 962 patients after aortic valve replacement as reported by Barnhorst et al.[64] An operative mortality of 6.3 percent is not reflected in this curve. The lower curve shows survival of patients with aortic stenosis treated medically as described by Rapaport.[83]

thetic valve. Hospital and late mortality rates with the Bjork-Shiley, Braunwald-Cutter, Lillehei-Kaster and Smeloff-Cutter valves have been shown to be similar,[81] and comparable to mortality rates for the Starr-Edwards aortic prosthesis[64] and the Smeloff-Cutter prosthesis.[82]

Late mortality seems to be more clearly associated with the preoperative status of the patient rather than the type of prosthesis. Heart size at the time of operation and the type of dominant aortic valvular lesions are more important in affecting late survival than the type of prosthetic valve.[64]

In considering the utility of aortic valve replacement it is useful to compare late mortality of aortic valve replacement with the natural history of aortic stenosis treated medically. A composite graph (Figure 9) has been constructed with operative mortality and late mortality reported by Barnhorst and co-workers[64] compared with those in a group of patients with aortic stenosis treated medically, as recently described by Rapaport.[83] The late mortality at nine years after aortic valve replacement was 27 percent compared with 78 percent in the group medically treated. (The surgical mortality excludes the low operative mortality.) Furthermore, in most patients in whom operations are done there is significant symptomatic improvement. Typical results were reported by Behrendt and Austen[51] of 113 patients in whom aortic valve replacement was done; most were New York Heart Association class III. After operation, 72 percent became class I and 28 percent class II.

In addition to thromboembolism and late valve failure, several other complications of aortic valve replacement require brief comment. Endocarditis involving the prosthetic valve is an extremely serious problem. This occurs in approximately 4 percent of patients[84] and if it occurs early is associated with a 79 percent mortality, compared with a 35 percent mortality if occurring after 60 days. Periprosthetic leak, with currently used prosthetic valves and techniques, is infrequent in the absence of infection. Poppet embolization, a disastrous complication, has also been reported,[53] but previous problems with poppet wear have been minimized in current prosthetic valves by appropriate selection of material. Cloth covering of the valve cage has also resulted in a significant degree of hemolysis as compared with the earlier Starr-Edwards valves,[85] and can occasionally be an important clinical problem.

Closing Remarks

DR. JOHNSON: *The management of patients with aortic valve disease remains a challenging problem, and requires the closest interaction among patient, physician-cardiologist and cardiac surgeon.*

In this conference, we have stressed the clinical features of aortic valve disease, contrasting aortic stenosis—with its triad of congestive failure, ischemic chest pain and syncopal episodes—with aortic regurgitation in which the onset of symptoms and myocardial damage is much more insidious.

The structural and functional abnormalities of the left ventricular myocardium caused by the pressure or volume overload, or both, accompanying aortic valve disease are important determinants of clinical symptoms and operative results, and their detection and prevention are therefore of paramount importance. Decisions regarding medical or surgical (or medical and surgical) management follow the accumulation of all pertinent historical, physical and laboratory data relative to the patient's disease process. This, added to the clinical information from noninvasive and catheterization studies, will allow a decision regarding the appropriate timing for valve replacement. We have emphasized the difficulty in identifying the optimum time for operative intervention in chronic aortic regurgitation, the requirement for careful medical management in this situation and the need for further investigation in this area.

In our opinion, valve selection at present would favor the use of the glutaraldehyde preserved porcine heterograft in all but the small aortic root because of its relative freedom from the need for anticoagulation and the low thromboembolic rate.

The long-term durability of this valve is currently unknown, however. When, for technical reasons, the use of the aortic heterograft is precluded, a variety of suitable prosthetic valves are available with the use of the tilting disc valves enjoying the most rapid rise in popularity.

Protection of the myocardium during operation is a most important factor in determining the success or failure of a given operation. That satisfactory operative results may be obtained with either continuous coronary perfusion or myocardial hypothermia has been shown by many series. With careful attention to the proper timing of operation, technical competence in valve replacement and adequate protection of the myocardium, the operative mortality should be less than 5 percent and, it is hoped, any significant insult to left ventricular myocardial function will be prevented.

With the gratifying progress in cardiovascular surgical techniques and results, it becomes all the more important for internists and cardiologists to identify and meticulously manage patients with aortic valve disease so that there can be optimal timing of surgical therapy to patients' clinical status and myocardial function.

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Refer to: The treatment of the nephritis of lupus erythematosus—Medical Staff Conference, University of California, San Francisco. West J Med 126:479-484, Jun 1977

Medical Staff Conference

The Treatment of the Nephritis of Lupus Erythematosus

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Associate Professor of Medicine, and H. David Watts, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, CA 94143.

DR. SMITH:* *Medical Grand Rounds this morning will focus on a difficult medical management problem common at this medical center. We have asked Dr. Wallace V. Epstein to discuss the treatment of the nephritis of lupus erythematosus.*

Case Presentation

DR. SLATER:† A 33-year-old Mexican-American woman was admitted to the University of California Medical Center in San Francisco for renal biopsy. The patient was well until November 1975 when she presented to another hospital with fever, leukopenia, anemia, arthralgias, an elevated sedimentation rate, and a positive antinuclear antibody test and lupus erythematosus cell preparation. Findings on urinalysis at that time were said to be normal and creatinine clearance was 82 ml per minute. Total serum complement was normal. A regimen of "high dose" glucocorticoids was started; there was remission in systemic symptoms but also problems of emotional lability and inability to concentrate, thought to be secondary to therapy. The administration of steroids was rapidly tapered to 20 mg of prednisone per day, and the patient continued in relative good health.

Proteinuria was first noted in December 1975. In April 1976 the patient was first seen in our Rheumatic Disease Clinic, and an antinuclear antibody test was positive at a 1:2560 dilution. Analysis of urine showed 3+ protein, red cells with occasional red cell casts. Creatinine clearance was 33 ml per minute. The serum complement level at that time was less than 10 CH50 units (normal value 25 to 42 units); erythrocyte sedimentation rate was 30 mm per hr (Westergren), and the patient was leukopenic. At the time of admission to this institution in July 1976 for renal biopsy, she continued to complain of arthralgias with occasional joint swellings, myalgias, occasional pleuritic chest pain and fatigue. She also complained of a continued inability to concentrate and lability of mood and emotion. She gave no history of seizures, dysuria, back pain, fever, edema or hypertension. Medication on admission included prednisone, 20 mg per day, aspirin, 15 grains every four hours, and multivitamins.

Her family history is remarkable in that several family members have an unspecified type of arthritis.

Pertinent physical findings included normal vital signs, no abnormalities on eye examination, supple neck, and clear chest. Cardiac examination showed no rubs or murmurs. There were no ob-

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†Evan Slater, MD, Chief Medical Resident.

ABBREVIATIONS USED IN TEXT

CNS = central nervous system
CSF = cerebrospinal fluid
DNA = deoxyribonucleic acid
NIH = National Institutes of Health
SLE = systemic lupus erythematosus

jective skin or joint findings and results of neurological examination were normal.

Laboratory data included urinalysis findings of 3+ protein, red cells, white cells and a few red cell casts. Urine culture was negative. The leukocyte count was 3,500 cells per cu mm, with 75 percent polymorphonuclear leukocytes and 18 percent lymphocytes. Hematocrit was 30 percent, reticulocyte count 1.2 percent and sedimentation rate 70 mm per hour. Total serum complement was less than 10 CH50 units; prothrombin time and partial thromboplastin time were normal. Urine light-chain concentration was elevated at 640 μg/ml (normal value <20). Antinuclear antibody was positive at 1:80 in a diffuse pattern. Serum antibody to native deoxyribonucleic acid (DNA) was 73.4 μg (normal value <1.5). Creatinine clearance at this time was 78 ml per minute. Twenty-four hour urine protein excretion was 2.2 grams. Blood urea nitrogen was 22 mg per dl, and serum creatinine was 0.9 mg per dl. An x-ray study of the chest and an intravenous pyelogram showed no abnormalities. A lumbar puncture was carried out with normal opening pressure. The cerebrospinal fluid (CSF) had six leukocytes per cu mm, all of which were lymphocytes. Glucose in the CFS was 60 mg per dl with a serum glucose of 94 mg per dl. CFS protein was 15 mg per dl. Results of brain scan were normal. An electroencephalogram showed an episodic slow wave disturbance.

An uneventful renal biopsy showed a diffuse proliferative glomerulonephritis, with segmental necrosis and a few crescents. Electron microscopy showed that the endothelial cells contained tubuloreticular inclusions in the cytoplasm and immune deposits in the mesangium. Because of the past adverse reactions to high doses of glucocorticoids, it was elected to continue administration of 20 mg of prednisone per day and to add chlorambucil beginning at 2 mg per day. This case is now being followed in the Rheumatic Disease Clinic.

DR. EPSTEIN:* The case just described presents little problem in diagnosing systemic lupus erythematosus (SLE), based on the clinical and laboratory abnormalities upon admission, despite several months of prednisone administration. It is, in fact, difficult to be certain whether the disease had been continuously active since its inception or whether we were seeing her during an exacerbation. Although few fields are so devoid of general agreement as is the management of lupus glomerulonephritis, it can be asserted that the combination of profound hypocomplementemia, a high titer of serum antibody to native DNA, high concentrations of urinary free light-chain protein and significant proteinuria indicate significant, active renal involvement despite the presence of a normal creatinine excreting ability. We have justified a renal biopsy in this patient because of its desirability for investigational as well as clinical management purposes. The biopsy specimen from this patient, as in about 70 percent of such patients in whom biopsy studies are done in this medical center, was interpreted as showing diffuse proliferative glomerulonephritis, the most unfavorable of the histological classifications.

A thorough review of past renal biopsy studies in patients with SLE that is being done by Drs. Hopper, Shearn and Biava shows that we see the minimal mesangial lesion in about 20 percent of patients at this institution. The Mayo Clinic group recently found neither minimal glomerular changes nor pure epimembranous lesions in the 39 patients with SLE included in their prospective treatment study.[1] In both centers, we probably see predominantly a disease subset manifesting the more severe and refractory problems.

Today we are less certain how to treat lupus glomerulonephritis than at any time in the past ten years. We can assert that glucocorticosteroid administration is effective and usually tolerated for relatively short periods in the management of nonrenal, noncentral-nervous-system systemic lupus. Although many flares of SLE can be managed effectively with salicylates, topical steroids, and perhaps antimalarials, almost without exception short-term administration of prednisone provides the most efficacious therapy for the extrarenal, extracentral-nervous-system problems of this disease. The occasional patient with an acute psychiatric reaction to steroid administration pre-

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sents the diagnostic dilemma of distinguishing drug side effects from central nervous system (CNS) lupus. Renal failure, CNS disease and superimposed infection together account for about 68 percent of deaths in SLE, with late deaths apparently more frequently caused by CNS and vascular involvement than by renal disease.

Even if our patient had not previously had an unfavorable reaction to prednisone, we would have three indicators of an unfavorable prognosis: (1) the renal biopsy showed generalized involvement with proliferative and sclerotic changes together with subendothelial deposits; (2) a combination of hypocomplementemia and high levels of serum antibody to native DNA was present; (3) we cannot be sure that the personality changes attributed to prednisone administration were not due to CNS lupus. As a result, our attention in this patient is directed more rapidly than is usual to the potential benefits of adding a cytotoxic agent.

Clinical experience with cytotoxic agents in SLE began in 1954, when Dubois administered nitrogen mustard to a patient with SLE and intractable nephrotic syndrome and reported rapid termination of massive proteinuria. During the 1960's, there was a limited number of similar patients treated with 6-mercaptopurine and 6-thioguanine; however, since then, the 6-mercaptopurine precursor, azathioprine, and the alkylating agents, cyclophosphamide and chlorambucil, have been used almost exclusively in attempts to alter the unfavorable course of lupus glomerulonephritis.

Clinical management trials at first centered on variations in the dose or frequency of administration of adrenocorticosteroids. Included in the studies by Pollack and co-workers[2] were high-dose versus low-dose therapy in which no clear benefit was noted at higher dose level. Baldwin, in 1970,[3] studied patients stratified according to the histologic features shown in the light microscope and studied prognosis when using high-dose prednisone therapy. He found that 50 percent of the patients with diffuse proliferative glomerulonephritis died within five years. Alternate day prednisone therapy and mega amounts used as pulse therapy have also been used but have limited applicability.[4]

It was probably the discovery of the New Zealand Black/New Zealand White murine model for SLE and the ability of cyclophosphamide to alter murine renal disease that redirected interest in studies of cytotoxic (immunosuppressive) agents in human SLE. In my view, this model also unfortunately led to the selection of cyclophosphamide as the alkylating agent of choice in clinical studies of both SLE and the more virulent forms of rheumatoid arthritis.

After ten years probably the only statement generally accepted is that the use of cytotoxic agents in the treatment of lupus nephritis must be regarded as investigational. Over the past ten years there have been steadily improving prognoses in patients having this disease. Several centers now report greater than 80 percent five-year survival rates for patients with biopsy-proven SLE diffuse proliferative glomerulonephritis.[5,6]

Donadio and his associates at Mayo Clinic[1] have noted a 30 percent improvement in prognosis when the two-year survival of their nephritic patients treated with prednisone plus cytotoxic drugs is compared with findings by Pollack[7] and his associates using prednisone alone. Indeed, when we examine the results from many centers caring for the most severely ill patients with lupus nephritis, something has improved their prognosis over the past decade.

In attempting to assess individual studies of therapy, and especially in trying to compare different studies, one must consider the question of disease stratification and sampling. Is the incidence of SLE in the community increasing, and how representative are the patients we treat?

Siegel's study in 1970[8] showed a rising incidence and prevalence figure between 1956 and 1965. Studies have shown a prevalence of 41.6 per 100,000 persons in Rochester, Minnesota, and recently, Fessel, studying records of the San Francisco Kaiser-Permanente hospital, found a prevalence of 51 per 100,000, and an incidence of 7.6 per 100,000.[9] The prevalence for women (especially black women) is more striking in the Fessel study. One in 700 women, ages 15 to 64, fulfill criteria for SLE, and one in 245 black women, ages 15 to 64, would appear to have SLE in the population reviewed, a frequency three times greater than their representation in the general population. The relatively benign nature of this condition in the community is indicated by a ten-year survival of over 90 percent and a finding of significant renal disease in only 11 percent of patients.

These facts concerning the disease in the community point to a first difficulty in studies of that subpopulation which makes its way to a univer-

sity medical center. We, like the University of California at Los Angeles, Mayo Clinic, Yale or the National Institutes of Health (NIH) Clinical Center, begin with a prestratified population emphasizing systemic severity, refractoriness to simple treatment, high frequency of significant renal and CNS disease, and special "soft" patient characteristics that may be important in preventing true randomization of cases in a therapeutic trial.

In most cases, the patients with SLE whom we see have either required corticosteroid therapy or require it soon after arrival. The extrarenal, extra-CNS problems of SLE usually respond to 15 to 25 mg of prednisone per day. For such problems the dose, frequency of administration and duration of therapy can be monitored effectively by clinical signs and symptoms, tests of organ function and the usual immunological determinations. It is a rare situation in which the refractory nature of these manifestations or the magnitude of undesirable drug effects requires consideration of adding an immunosuppressive drug. We can, therefore, turn our attention to the treatment of lupus glomerulonephritis and consider why we are still uncertain whether the combination of prednisone and a cytotoxic agent is more effective therapy than is prednisone alone.

Cameron[10] reviewed the course of approximately 233 patients with lupus nephritis seen between 1963 and 1970 who were treated with one or more of six alkylating agents or antimetabolites. Ten percent of treated patients had remissions, 30 percent improved and 50 percent were either unchanged or worse.

The vast majority of investigators conducted uncontrolled studies. A summary of their barely controlled enthusiasm (see Table I in reference 11) suggests why either azathioprine or cyclophosphamide, or in a very few centers, chlorambucil, was added to the regimen of patients found refractory to prednisone alone or of patients in whom the side effects of sustained high-dose prednisone were found unacceptable.[11]

Some of the major difficulties encountered in attempting to aggregate these uncontrolled studies include:

- Differences in how survival figures were calculated; for example, from different starting points such as first rash, or first proteinuria or diagnosed SLE, or date of renal biopsy.
- Differences in the duration of the disease before adding the specific agent being evaluated for efficacy.
- Differences in study end points; for example, survival, change in creatinine clearance, change in renal biopsy.
- Differences in interpretation of the renal histologic features as well as a changing classification of the renal lesions of SLE.
- Differences in the mode of administration of medication; for example, fixed dose, variable dose, sliding scales.
- Differences in criteria for changing dose level or withdrawing medication.
- Case exclusion criteria; for example, patients with creatinine clearance less than 20 ml per minute for three months were or were not excluded from the study.

I detail these criticisms of the uncontrolled studies because these same issues becloud the few controlled studies we must consider next.

As the pejorative quality of the word "uncontrolled" gradually increased, more attention was directed toward the few controlled studies. Two studies, limited to azathioprine and cyclophosphamide plus prednisone, were reported in the November 1975 issue of the *Annals of Internal Medicine*. That volume contains the 28-month follow-up of the NIH controlled study of both of these cytotoxic agents[12] as well as a controlled study by Hahn and associates using prednisone and azathioprine.[13] In the August 1976 issue of the *Mayo Clinic Proceedings* we find a study of prednisone and cyclophosphamide by Donadio and co-workers.[1] In considering these three prospective, controlled studies, we must first examine the design of randomized, prospective, controlled studies in multifactorial, poorly defined, chronic diseases, and ask whether such a study is really possible in SLE.

In order for the administration of a cytotoxic agent to be the main variable, the drug recipients —that is, the cases of SLE—must be homogeneous. SLE, even when stratified by the morphology of the renal biopsy, is one of the most heterogeneous of the rheumatic diseases as evidenced by the emergence of several clinical and serologic subsets; for example, mixed connective tissue disease.

Hecht,[14] in trying to detect prognostic indices in lupus nephritis, made the treated population more homogeneous by limiting consideration to subjects showing a similar renal lesion by light microscopy and subendothelial deposits by electron microscopy. On treating 31 such patients with prednisone and azathioprine, he found that

12 improved, 11 deteriorated and 8 remained the same. He felt able to relate response to therapy with whether or not the subendothelial deposits disappeared on repeat renal biopsy.

As Feinstein[16] so aptly points out:

> Unless the prognostic differences of the patients are appropriately identified and classified, the treatment will be allocated indiscriminately to "good risk" and "bad risk" cases whose basic differences are left unrecognized. This type of promiscuous randomization may remove bias in the assignment of treatment, but it also removes clinical sense in the evaluation of results. The results will be clinically meaningless, because a clinician will not know how to apply them in the future; he cannot determine whether "good risk" and "poor risk" patients responded the same way to each therapeutic agent. The results may even be clinically misleading, because agent A and agent B may have exactly the reverse therapeutic effects in "good risk" and "bad risk" patients, but the differences will be obscured when all of the results are added up in a grand statistical conglomeration that ignores prognostic differences.
>
> Aware of prognostic heterogeneity in patients, some statisticians attempt to stratify the treated population into "comparable" groups. The trouble with most of these stratifications is that the "comparable" groups are usually selected according to the demographic features of age, race, and sex, instead of the clinical and paraclinical phenomena that are harbingers of prognosis. The problems of a suitable correlated prognostic stratification currently constitute one of the major scientific obstacles that impede statistical and clinical progress in the design of therapeutic trials.

In the report by Donadio and co-workers,[1] claiming to show that cyclophosphamide and prednisone offer no advantage over prednisone alone, they report that after six months of therapy, seven patients were worse—four receiving prednisone and three receiving prednisone plus cyclophosphamide; but all seven were admitted to the study having moderately to severely impaired renal function.

If we examine their results beyond six months (average 74-month survival), we note that in seven other patients there was progression of disease, only one of these had received both cyclophosphamide and prednisone. Therefore, it would appear that had established renal failure been used as an exclusion criterion, this study would have suggested a benefit from the combination of the two drugs. A previous study by this same group in 1974 indicated no benefit accrued from the combination of azathioprine with prednisone as compared with the prednisone alone.[18]

In the study by Hahn and co-workers[13] randomization of a small number of patients resulted in six of the nine patients in whom renal biopsy was done and who were treated with prednisone alone having either a minimal mesangial or a pure membranous lesion—that is, only three of 13 in the group treated with prednisone alone had a proven diffuse proliferative lesion. In nine of the 11 patients who received prednisone plus azathioprine, a diffuse proliferative lesion was shown by biopsy (including three with focal changes beyond the mesanginum). This, again, illustrates the probable advantage of selective stratification before attempting randomization.

The NIH controlled study using either azathioprine or cyclophosphamide with prednisone terminating in a negative report[19] was disappointing, since the early studies of this group of patients were favorable,[17] especially for patients treated with cyclophosphamide. A detailed critique of the 38 patients followed for 2½ years in the NIH study is not possible here, but a theme developed in several of the letters to the editor[18,19] that appeared following the NIH group report. The letters stressed the nonrandomization of important co-morbidity factors, and the small size of the subgroups that developed as the toxicities, especially using cyclophosphamide, resulted in shifting patients from one regimen to another. In fact, Table 7 of the report shows that in only two of the 16 patients who received either of the immunosuppressive agents did renal failure develop (one died), while in five of 13 who received prednisone alone there was an unfavorable course, three dying from hemopsychiatric related causes and renal failure requiring dialysis developing in two. Further, a more impressive reversal of anti-DNA antibodies and reduced serum complement was noted by the authors when using immunosuppressive agents rather than prednisone alone. Dr. Barnett of the group at the University of California at Los Angeles reacted in his letter to the editor[18] by recording no deaths due to renal disease in 55 patients with diffuse proliferative glomerulonephritis treated with corticosteroids and azathioprine and followed for at least five years.

I would like to conclude with a few words on our therapeutic approach and some attributes that should go into any attempt to stratify patients so that differences in responses are attributable to therapeutic maneuvers. I avoid the use of the term "randomization," since that may not be possible in the study of a chronic multifactorial disease such as SLE.

Using historical controls based on renal biopsy and duration of detectable renal disease, we have in previous studies showed a highly significant

improvement in outcome compared with studies by Baldwin and associates in patients with diffuse proliferative glomerulonephritis.[5] We have no fixed dose schedule but use the least amount of prednisone in divided doses that reverses defined clinical and laboratory abnormalities. The criteria upon which a patient is designated as a prednisone failure, and therefore in whom chlorambucil therapy is added, are somewhat variable. Our present efforts to define precisely "good risk" and "poor risk" subsets include refinement of light, electron and fluorescence microscopy; special serologic characteristics including the antibodies to extractable nuclear antigens and L-chain proteinuria, as well as the more obvious elements of duration and degree of renal excretory impairment. We are turning to the addition of chlorambucil earlier and in smaller amounts than in previous years.

The conceptual and technical basis of therapeutics research in multifactorial, chronic diseases may not have evolved sufficiently to address these several issues. The few so-called controlled studies have not provided an unequivocal answer. We look forward to the pooling of patient populations from several centers to provide us with the relatively homogeneous disease subsets that are necessary before improved therapeutic experiments can be undertaken.

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Important Advances in Clinical Medicine

Epitomes of Progress — Nuclear Medicine

The Scientific Board of the California Medical Association presents the following inventory of items of progress in nuclear medicine. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in nuclear medicine which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Nuclear Medicine of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, California Medical Association, 731 Market St., San Francisco, CA 94103

Oral Contraceptives, Hepatic Adenomas and Liver Scans

SEVERAL RECENT REPORTS link oral contraceptive steroids (OCS) to the formation of benign hepatic adenomas in young women. Although histologically benign, the variable clinical course includes spontaneous rupture and hemoperitoneum. This catastrophic event, when not immediately fatal, substantially increases the surgical mortality. Liver scanning with multiple agents is an important modality in the noninvasive diagnosis of these lesions.

The usual liver scan using a colloidial agent is the first scan which should be done. This scan shows the distribution of reticuloendothelial cells. Hepatic adenomas consist of sheets of hepatocytes and do not contain Kupffer cells. The colloid scan will show tumors which are at least 2 cm in size as defects or holes in the liver. This study should be done on patients at risk with an enlarged, painful or tender liver. It might even be considered as part of the periodic evaluation of patients on a long-term regimen of OCS.

Two other scans which are helpful in the detection of these tumors are gallium citrate Ga 67 and ^{131}I rose bengal. When yielding abnormal findings, they lend same specificity to the lesions seen on colloid scans. The hepatocytes of the benign adenoma may be sufficiently differentiated to concentrate rose bengal. Soon after injection, the radioactivity clears from the normal liver parenchyma via the biliary system. Due to the absence of biliary radicles in the adenoma, the rose bengal is not cleared and delayed scans may show radioactivity in the cold area of the colloid scan.

Gallium is taken up by normal hepatocytes to a limited degree. Notably abnormal cells with a high lysosomal activity as found in the malignant forms of primary liver tumor concentrate gallium in greater amounts. Benign hepatic adenomas, although containing some gallium, usually have a lower concentration and appear as cold defects in the liver which can differentiate them from the malignant forms.

Therefore, the constellation of findings in a patient on OCS pointing towards the diagnosis of benign hepatic adenoma are cold defects on a colloid liver scan which show no significant gallium concentration but retain rose bengal.

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Radionuclide Techniques for Detection of Occult Abscesses

THE DIAGNOSIS of occult abscess is still a clinical enigma. Various isotopic techniques including static imaging and dynamic flow studies have been used with variable results. Combined liver-lung scans are used to detect subphrenic abscesses but are unreliable in the presence of ascites and basilar lung diseases. Blood pool agents may outline larger abscesses as avascular masses. This method, however, lacks sufficient sensitivity.

Recently, leukocytes labeled with chromium 51 (^{51}Cr), technetium Tc 99m sulfur colloid (^{99m}Tc-SC) and gallium citrate Ga 67 (^{67}Ga) have been used. ^{51}Chromium-labeled leukocytes produce images that are less than ideal due to the intense background activity resulting from margination of leukocytes along the vessel walls. ^{51}Cr labeling may also impair leukocyte function. ^{67}Ga-labeled leukocytes will localize in abscesses which are only 3 to 14 days old. Advantages of ^{67}Ga-labeled leukocytes are that incisional abscess can be detected and there is less background activity in the reticuloendothelial system making abdominal lesions more apparent. However, low count rates and nonspecific labeling restrict its clinical usefulness. ^{99m}Tc-SC-labeled granulocytes offer some promise since they are viable *in vivo* and retain both chemotactic and phagocytic properties. This technique is sensitive but gives false positive results in the presence of thrombi. ^{99m}Tc-SC-labeling allows early scans to be done, which is a benefit in extremely ill patients.

Gallium citrate Ga 67-scanning is the most common and tried isotope procedure for the detection of inflammatory lesions. Scans done at 24 to 72 hours will show most of the active infections. Unlike the localization of gallium in tumors, concentration in abscesses occurs rapidly allowing scans to be done as early as two to four hours after injection. The early scans have the added advantage of minimal gallium excretion in the colon making it easier to detect abdominal lesions. The uptake of gallium by abscesses is dependent on the inflammatory activity and number of leukocytes. The concentration diminishes with response to chemotherapy. The state-of-the-art when searching for obscure infections is to do early (about 4 hours) scans followed by delayed images. A positive study, however, is nonspecific and abnormalities will be seen in tumors, granulomas and surgical wounds. Clinical correlation is necessary to differentiate among these possibilities.

The gallium citrate Ga 67-scan still remains the most popular technique. Leukocyte labeling is highly technical and still in the experimental stage. It is possible that combined studies using gallium citrate Ga 67 and labeled leukocyte will eventually be the preferred approach in achieving maximum sensitivity and specificity.

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Large-Field versus Conventional Scintillation Cameras

SODIUM IODIDE SCINTILLATION CRYSTALS, the core of detector systems in nuclear medicine, are produced by "growing" them from their center. Their size is restricted by the expense of the manufacturing process and the frequent appearance of defects with increasing size. In the past ten years, scintillation cameras used clinically have been limited to crystals with an effective viewing area of about 10 inches in diameter. Recent advances in crystal technology, however, have enabled manufacturers to make available commercially scintillation cameras with a field of view of up to 15 inches.

In comparison with conventional scintillation cameras, large-field scintillation cameras have substantially increased sensitivity for equivalent amounts of radioactivity, with only a minimal sacrifice of resolution (pictorial detail). Large organ areas, such as both lungs or liver and spleen together, can be visualized on a single image with better sensitivity and resolution than with the older devices. The large-field cameras are particularly suited for ventilation studies with radioactive gas. These have to be done during

breath-holding or specific phases of the respiratory cycle; the greater sensitivity of the larger crystal permits three to four times more photons to be counted in the same frame. The better photon statistics improve the resolution and reduce motion artifacts.

The same considerations apply to other dynamic studies with rapid sequential time framing. Smaller structures, such as brain or heart, can be imaged with a "converging collimator." In this device, the holes in the lead shield between patient and detector are not parallel as usual but converge to a point in the distance. This permits preservation of good sensitivity and resolution but introduces a slight parallax effect which can be easily compensated by an experienced interpreter.

Another area in which large-field scintillation cameras have proven particularly useful is whole-body imaging for bone scanning or gallium scanning. The combination of a large-field camera and an automated moving table produces high quality whole-body images much more rapidly and effectively than with other types of equipment.

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The Value of Radioisotope Venography

PERFUSION LUNG SCANNING is widely accepted and used in medical practice because of its safety, ease and sensitivity in the detection of acute pulmonary embolism. Radioisotope venography is an adjunctive procedure to lung scanning in patients in whom deep venous thrombosis or pulmonary embolism is suspected. The lung scanning agent technetium 99m labeled macroaggregated albumin or microspheres is injected into both dorsal pedal veins rather than the usual arm vein injection site. By imaging over the lower extremities during and immediately after injection, one can evaluate the patency of the major deep venous system and visualize the presence of abnormal collateral venous drainage with good reliability and accuracy. This can be followed immediately by perfusion lung scanning.

Additional information may be gained by a second series of images of the lower extremities following the lung scan to identify areas of prolonged particle stasis or entrapment distal to sites of venous occlusion.

Due to the inadequacy of any single method, many tests have been and are being developed for detection of deep venous thrombosis with various degrees of sensitivity and accuracy. None of the other methods will assist in determining whether the critical and often silent complication of pulmonary embolism has taken place. The radioisotope venogram as an adjunct to the perfusion lung scan often will provide important information necessary for clinical management and either preclude or strengthen the necessity for other more definitive procedures such as contrast phlebography or pulmonary angiography with their added attendant discomforts and risks.

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Regional Myocardial Perfusion Analysis with Thallium Chloride 201

WHEN INJECTED INTRAVENOUSLY, thallium, like potassium, is taken up by the myocardium according to the distribution of coronary blood flow. The emission characteristics of its isotope thallium 201 are better suited for high resolution imaging with the newer scintillation cameras, than those of the radioactive forms of potassium. Because after extraction from the blood the tracer remains in the myocardium without significant redistribution for many minutes, multiple scintigraphic images from multiple angles can be obtained.

Regional decreases in myocardial perfusion are seen as "cold" areas within the myocardial image. Perfusion abnormalities have been shown scintigraphically in acute myocardial infarction, regional myocardial ischemia, right ventricular hypertrophy, asymmetrical septal hypertrophy and in scarred myocardium or ventricular aneurysms. The reproducibility of the technique has been well established.

Although patients with ischemic lesions usually present with angina and abnormal findings on a stress electrocardiogram (ECG), ischemic lesions

have also been shown when results on a stress ECG were ambiguous or, conversely, when there were abnormal stress ECG findings in an asymptomatic patient. The correlation with anatomical abnormalities of the coronary arteries is good, but not absolute. Ischemia can be due to, and has been shown to occur in, coronary artery spasm, prolapsing mitral valve syndrome and asymmetrical septal hypertrophy.

A perfusion defect can also be found in acute myocardial infarction, but the lesion cannot be differentiated from scar and fibrosis due to old disease.

To show the presence of ischemic lesions, a two-part examination is done. In the first part, the tracer is injected intravenously at the time of maximal exercise. If the myocardial image is normal, no other scintigraphic procedure is required; if it is abnormal, a rest study is done at a later time. Defects present both at rest and exercise are considered due to old damage. Those present only with exercise are classified as ischemic lesions.

In summary, regional myocardial perfusion can be evaluated with ease in a variety of circumstances using thallium chloride 201. The procedure is noninvasive, sensitive and reproducible, and undoubtedly will be applied in showing perfusion abnormalities in a variety of circumstances as experience with the technique is gained.

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Radionuclide Imaging in Metastatic and Metabolic Bone Disease

RADIONUCLIDE BONE IMAGING has proved to be a useful diagnostic test for the early detection of metastatic bone disease. During the past three or four years with the advent of technetium-99m-labeled phosphate agents, bone imaging procedures are now generally available in the medical community. It has been shown that with these newer agents the sensitivity of metastatic bone lesion detection by means of radionuclide imaging approaches 98 percent. In contrast, skeletal radiographic studies show less than 50 percent of lesions. However, since the abnormalities detected by radionuclide imaging are not specific for any particular disease, it is advisable to correlate these findings with all available clinical data, especially results of radiographic studies.

Although bone imaging has been extensively used for the detection and evaluation of metastatic bone disease, primary bone tumors, fractures, osteomyelitis and arthritis, the value of this technique in the detection and evaluation of bone lesions due to metabolic bone disease such as primary or secondary hyperparathyroidism has been recognized only recently. A recent study has shown that radionuclide bone imaging is more sensitive than radiography or bone calcium estimations by photon absorptiometry in the detection of bone lesions associated with metabolic disease. Such lesions, in contrast to neoplastic lesions, are more commonly located in the distal appendicular skeleton. It should be noted, however, that the abnormalities detected by radionuclide imaging in metabolic bone disease are similar to those associated with metastatic neoplasm and therefore they must be correlated with clinical data including radiographic findings.

In summary, radionuclide bone imaging is a superior diagnostic test, not only for the detection of metastatic bone disease but for the detection and evaluation of metabolic bone disease as well. The bone scan is the most sensitive indicator of skeletal disease. Conversely, an imaging study that shows no abnormalities usually excludes the presence of skeletal disease. Less than 5 percent of bone metastases will be undetectable by scan.

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Radionuclide Studies of the Hip

A PAINFUL HIP and the need to evaluate the vascular supply to the femoral head are the usual reasons for requesting a radionuclide study. Two common techniques are (1) hipbone image, using technetium Tc 99m diphosphonate or a related technetium-phosphate compound and (2) bone marrow (BM) of the hip image, with technetium Tc 99m sulfur colloid, using the BM activity as an index of perfusion. Simultaneous

imaging of the hips allows comparison of right and left hip activities. Perfusion is considered absent if activity in the region of the femoral neck is below adjacent body background, probably present if activity equals background, and normal for increased activities. Bone activity is considered normal if activity in the region of the femoral head is equal to, or only slightly greater than, surrounding bone activity. Abnormal activity may be less than, or distinctly greater than, surrounding bone activity. Changes from a baseline value are also considered significant.

Infarcted bone undergoes a sequence of changes. Acutely there is simply the avascularity (negative area on bone scan); after several days there is an increasing osteoblastic reactivity surrounding the ischemic-avascular bone (bone scans become increasingly positive) over a period of weeks. The BM image shows decreased perfusion of the neck during the entire sequence. If revascularization occurs, commonly seen in Legg-Perthes disease, the BM study will show increasing activity and the bone study will return to normal.

Therefore, in patients with chronic avascular necrosis there will be a negative BM image and a positive bone image. This pattern would be expected also with trauma, sickle cell crises and tumors (and probably osteomyelitis). On the other hand, in a patient with osteoarthritis, frequently the major differential diagnosis in hip pain, there will be parallel changes in bone and BM activity, both increasing if there is active inflammation, both decreasing if there is relative disuse of the involved joint.

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Serum Ferritin

FERRITIN, the second most abundant iron protein in the body, can be measured in serum by means of a radioimmunoassay. Serum levels are proportional to the size of the body iron stores. They are more accurate indicators of iron deficiency than serum levels of iron or iron binding capacity or bone marrow aspirates stained for hemosiderin. As expected, mean values are higher in men than in women, but in either case—and regardless of age—serum values under 12 ng per ml are almost invariably diagnostic of iron deficiency. Levels above 50 ng almost always exclude iron deficiency in the differential diagnosis of anemias. Each ferritin molecule is thought to consist of a ferric iron hydroxide phosphate core and a protein shell with a molecular weight of about 450,000. Found mainly in the cytoplasm of reticuloendothelial and liver cells, it is assumed to be an iron storage protein and regulator of iron metabolism. From a practical standpoint, the finding of an elevated serum ferritin level in an anemic patient would exclude iron deficiency and might obviate the need for bone marrow examination.

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Lung Scanning and the Detection of Pulmonary Emboli

Combined 81m-Krypton Ventilation/99m-Tc-macroaggregate Perfusion Scintigraphy

INTRAVENOUSLY INJECTED PARTICLES whose diameters range from 15 to 50 μ are carried through the right atrium and ventricle, and distribute themselves over the lung capillaries according to blood flow distribution. In the capillaries they remain trapped for an average of 30 minutes to 4 hours. If the particles are labeled with a gamma emitting isotope, the distribution of the blood flow to the lungs can be estimated by scintigraphy. therefore, perfusion abnormalities can be detected as "defects" in the scintigram.

But do perfusion defects represent pulmonary emboli? Not always, and the question has been argued with some passion over the years. Normal findings on perfusion scintigraphy almost eliminate the chance that a pulmonary embolism will be found, but all perfusion defects are not indicative of the presence of pulmonary emboli. On pulmonary angiography, emboli will be found respectively in 81 percent, 50 percent and 9 percent of cases with lobar, segmental and subsegmental defects shown on the perfusion scan. The specificity of the test increases if it can be shown that the corresponding lung lesion has a normal ventilation. In those cases the probability of finding emboli by angiography becomes 94 percent,

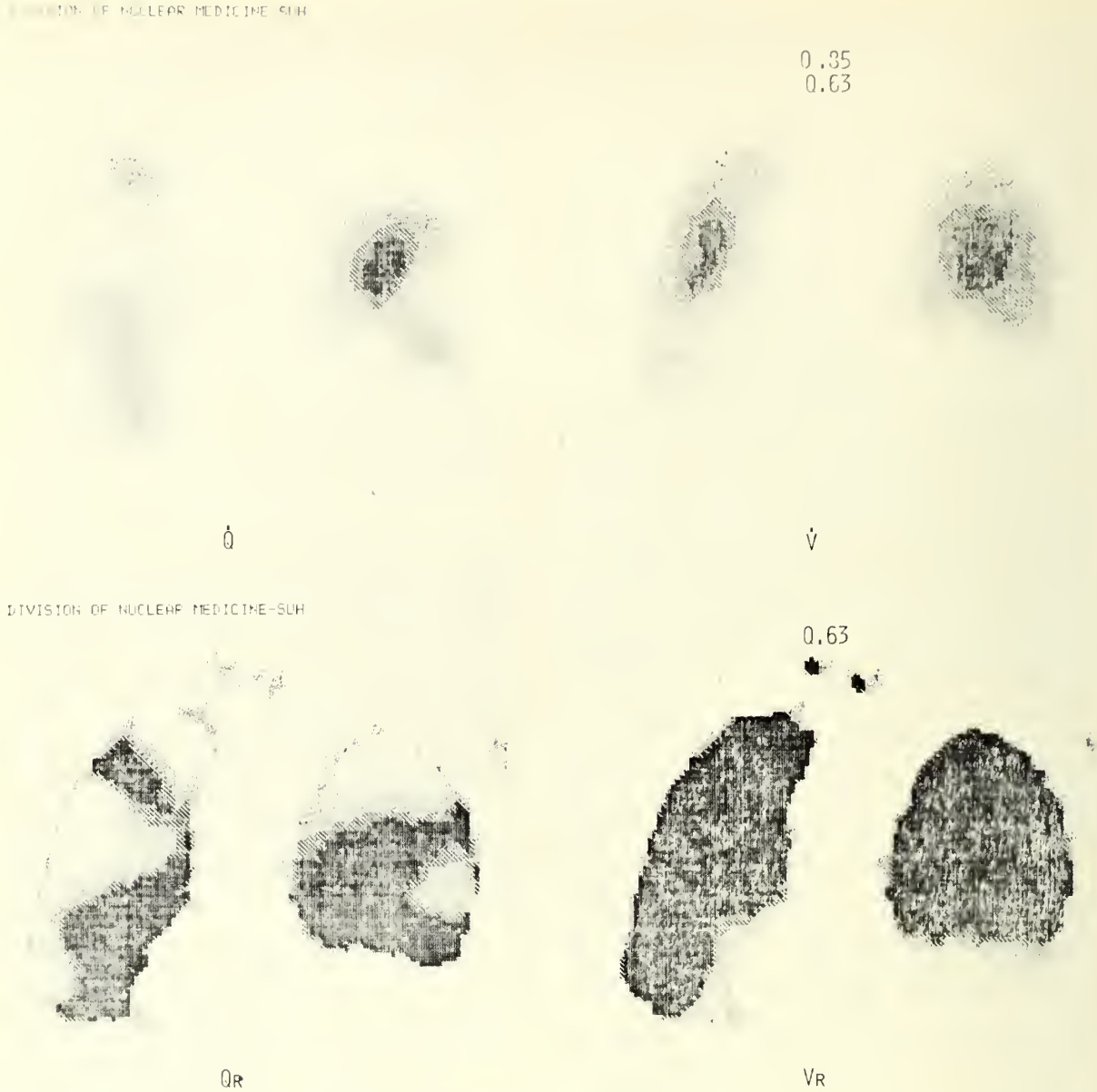

Figure 1.—Ventilation perfusion lung scan, posterior view.
The top part of the picture shows the perfusion study on the left, the ventilation study on the right. The right diaphragm is elevated. Additionally, multiple segmental defects are seen in the perfusion study, without corresponding abnormalities in the ventilation picture. This is underscored in the pictures at the bottom. On the left a perfusion/ventilation ratio shows the multiple perfusion defects, while on the right a ventilation/perfusion ratio shows that there are no isolated ventilation abnormalities.

100 percent and 50 percent respectively. If the perfusion defects are matched by ventilatory abnormalities, only 11 percent represent an embolus.

Recently a new technique has been introduced that greatly simplifies the determination of regional lung ventilation. In this technique a very short-lived (13 seconds) radioactive inert gas (81m-krypton) is inhaled by the patient. The short life of the tracer prevents it from reaching less ventilated regions, so that its distribution reflects lung ventilation exactly as the distribution of the particles reflects perfusion.

In normal cases the ventilation and perfusion images are very similar. Mismatches between ventilation and perfusion can easily be detected (Figure 1).

The new method is less cumbersome than the previous methods and allows the alternating recording of ventilation and perfusion scintigraphies, thus avoiding the need for repositioning. Little

patient cooperation is needed so that the method can be applied to sick persons. Finally, the method appears sensitive enough to weaken the argument that mismatches are in fact due to the lack of sensitivity of the method used to detect regional ventilatory abnormalities.

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The Use of Bone Scans in Benign Disease of Bone

SIGNIFICANT ADVANCEMENT in nuclear medicine instrumentation and radiopharmaceuticals has resulted in the widespread use of bone scans. A number of excellent publications have stressed the sensitivity and reliability of bone scanning in the detection of occult malignancies. Recent articles also have stressed the value of bone scans in a number of benign conditions.

- *Acute Osteomyelitis.* In patients with bone pain and fever, abnormal findings on bone scan may be the only sign of osteomyelitis. In general, the bone scan in these patients becomes positive within 48 to 72 hours after onset of symptoms.
- *Trauma.* Bone scanning has been shown to be a sensitive indicator of trauma to the skeletal system. Not only are major bone fractures visualized, but small stress fractures that are x-ray negative may be seen.
- *Paget Disease.* The extent of Paget disease can be readily determined from the use of total body bone scans. The response to therapy may also be studied and quantitated using scanning techniques and computers.
- *Benign Tumors.* Benign bone tumors such as osteoid osteomas can be detected using conventional bone scanning techniques.
- *Joint Disease.* Scanning of the arthritides, especially rheumatoid arthritis and osteoarthritis, as well as septic arthritis, is useful in determining the site as well as the extent of involvement.
- *Other Diseases of Bone.* Bone scanning coupled with marrow scanning has proven to be of value in the assessment of bony infarction, Legg-Perthes disease, metabolic disease of bone and other less common diseases of the skeletal system.

In summary, recent advances in radiopharmaceuticals and instrumentation have made possible the evaluation of a number of benign diseases of the skeletal system with a low degree of radiation exposure, and high degree of reliability and safety.

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Soft Tissue Accumulation of Bone Scanning Agents

SCINTIGRAPHY with various technetium-phosphate compounds (TcP) is very useful in the diagnosis of benign and malignant bone disease, and its superior sensitivity compared with radiography is well documented. Like any medical technique, however, it has its shortcomings. These include lack of specificity, occasional false-negative results and also extraosseous radiopharmaceutical localization, which may or may not interfere with interpretation of the study.

While not all causes for soft-tissue uptake are known, a number have been described. They include:

- Physiologic concentration in the urinary tract, since TcP is excreted by this route. This permits, from time to time, detection of unsuspected genitourinary pathology.
- Poor quality of the radiopharmaceutical, leading to concentration of free technetium in thyroid and stomach or to colloid aggregation and phagocytic uptake in liver and spleen.
- Increased tissue calcium levels, as in necrotic and acutely damaged muscle and in some calcifying neoplasms and granulomas (sarcoid). The high TcP concentration in acutely infarcted myocardium has been turned to advantage for detection and localization of acute myocardial infarcts. Even slight skeletal muscle damage, due to repeated intramuscular injections, may result in prominent TcP deposition.
- For reasons still unknown, normal breast tissue and a number of soft tissue tumors without demonstrated abnormalities in calcium metabolism will also concentrate TcP, particularly carcinoma of the lung, breast and colon and sarcoma.

Unusual extraosseous TcP concentration (outside of the genitourinary tract) is seen in about 10 percent of all bone scans. To avoid confusion and unnecessary repetition of procedures, nuclear medicine specialists and referring physicians have to be aware of its occurrence and causes.

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Radionuclide Studies in Peripheral Arterial Disease

TWO RECENT important clinical applications of radionuclide studies in the evaluation of peripheral arterial disease have been described. The first, described by Siegel, involves the use of intraarterially injected ^{99m}Tc human serum albumin microspheres as means of visualizing and quantifying the inherent hyperemic response which would be necessary for an "ischemic ulcer" to heal. The procedure is analogous to a lung scan in that the distribution of the microspheres is proportional to the distribution of perfusion. If, after point counting over the ulcer and the surrounding tissue, the relative hyperemia of the ulcer to the surrounding tissue is equal to or greater than 3.5:1, then there is a 90 percent probability that the ischemic ulcer will heal with conservative measures. However, if this degree of hyperemia is not present, there is about a 90 percent probability that healing will not occur and an amputation will eventually be required. It is anticipated that the procedure will prevent an unnecessarily prolonged stay in hospital and premature surgical procedures.

The second application is the use of isotopically derived skin perfusion pressures as a prognostic indication of postamputation skin flap healing. Lassen, using intradermally injected tracer amounts of a ^{131}I-antipyrine-histamine mixture, has developed a simple method to determine local skin perfusion pressure. An external pressure system is applied with force just sufficient to stop tracer washout from the region. This pressure is recorded as the skin perfusion pressure.

It has been noted that all skin flaps with pressures below 20 mm of mercury fail to heal, while none of those with pressures greater than 40 mm of mercury fail to heal because of ischemic necrosis. The region between 20 to 40 mm of mercury is considered an undeterminant zone. As in the first procedure described it is anticipated that the approach will help avoid premature reamputation or unnecessarily prolonged stays in hospital.

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EDITORIALS

Health Care Costs — A Call for AMA Leadership

ONCE AGAIN we welcome the American Medical Association to San Francisco and the West for its Annual Convention—an event which is without doubt the most important medical meeting held in America. This year there is a special sense of urgency and some real alarm. Our health care system seems to be rushing at breakneck pace along a course that can only lead to some kind of disastrous consequence. The disastrous end point is beginning to become apparent. In the not too distant future the rising costs of the nation's health enterprise will equal or exceed the portion of the gross national product (GNP) that can be available for this purpose. In the opinion of some responsible persons this will happen when health-related costs reach approximately 9 percent of the GNP. They have now reached 8.6 percent and continue to grow.

The specter at the end of this road is an arbitrary and enforced cap on health costs with inevitable restrictions on the freedom of doctors and patients, and on what patient care services will be available to whom—paradoxically, quite the opposite of the goal of equal access to high quality health care for all.

Industry, labor, government and the public are all becoming profoundly concerned, and with good reason. Health care costs cannot be permitted to unduly distort the nation's economy. When health care costs began to rise precipitously government tried various approaches to control them. The results were poor, and many if not most of the efforts turned out to increase costs. The time seems to be rapidly approaching when drastic action may be expected—unless there is an alternative.

The private sector, and particularly organized medicine, has stood on the sidelines until very recently. In 1976 the AMA established a National Commission on the Cost of Medical Care and in 1977 the House of Delegates of the California Medical Association voted to create a Commission on Health Care Costs to study what might be done. Elsewhere in this issue E. Kash Rose calls upon physicians themselves to do something about it *now*. Physicians really control how, and for what, much—perhaps most—of the money is spent in patient care. Physicians can do a great deal if they develop a genuine interest in controlling costs and a genuine determination to do so. There are the simple things, such as asking whether the benefit to be derived from a test or procedure is really worth the cost. But we can probe deeper. As yet there has been little or no real assessment of the effectiveness of much of what we do in relationship to its cost. And there has been little if any assessment of the predictable ramifications in costs of many new discoveries, new innovations or new practice procedures.

To do this is in the best interest of physicians as well as of the public. Unless something is done quickly in the private sector the government will soon have no alternative to imposing a crude and even brutal cap on the money spent. Health care could even become a jungle. Yet who in the private sector is capable of providing the necessary leadership? We look to the AMA. We have no alternative. Will the leadership be given? We hope so. What is at stake is something grand—something above us all: it is American medicine's record of freedom for both doctor and patient, of excellence in patient care.

Time is running out. This is a call for AMA leadership before the opportunity is gone.

—MSMW

The Federal Trade Commission and Health

THE PRIVATELY FUNDED National Health Council recently published a special report on "The Federal Trade Commission and Health" which gives an account of some of the actions of the Federal Trade Commission (FTC) during the last year or two. These are of the greatest concern to physicians, to other professionals and in the long run to the public as well. The FTC actions do nothing less than strike at the heart of the role of the professions in American society. The FTC appears to view the professions as trades which are to be regulated by the rules of the marketplace. For medicine this gets down to whether the standards—which really means the quality—of professional education and professional practice is a primary responsibility of the profession as it has been considered up to now, or whether these should reflect the free competition and the trade practices of the marketplace. The other professions against whom the FTC has been taking similar actions are similarly threatened.

What is at issue is nothing less than what is to be the function of the professions in the complex interdependent technologic society that America has become. Is there a need, or is it desirable, for segments of society to develop special knowledge, skills and expertise in certain subject matter (which we know as professional disciplines) which are necessary for the orderly conduct of society, but which may be beyond the interest or understanding of every citizen? And if this is the case, should these segments of society (which we know as the professions) have some control over the content and practice of their special disciplines or should this be governed entirely by the rules of the relatively uninformed free market? It seems unlikely that the FTC has addressed these fundamental questions, or even considered what might be the long-range social impact of the course upon which it has evidently embarked. There certainly has been no open discussion of the possible or likely far-reaching consequences of which we are aware.

The FTC is an independent federal regulatory commission created in 1914 to protect consumers and businessmen from unfair competition and unfair trade practices. Its legal powers include administrative, legislative and judicial authority. It can make its own investigations, issue its own orders which have the force of law, enforce its own orders, conduct its own litigation and represent itself in court. It has its own administrative judges who pass on disputes. One can appeal an FTC action outside its system only after one has been through the cumbersome legal machinery of the system itself, which can take years and for many be a prohibitively costly process as some professional associations have already discovered —and having found it out, have capitulated to FTC pressure. In recent years the FTC hand has been greatly strengthened by a number of Supreme Court decisions and by increasing support from Congress. There is good reason to believe that it is now beginning to respond to the increased consumer activism of the times, in this case consumer activism in the health field.

It is easy enough to see how health and health services would seem to be a natural target for a revitalized FTC. The portion of the Gross National Product consumed for health services is large and continues to grow. The inflation rate for health and medical care is significantly greater than that for the economy as a whole, at least raising the question of artificial constraints operating to raise prices. Many characteristics of the system appear to be disproportionately controlled or influenced by relatively few participants, and the system is so structured that cost consciousness seems relatively nonexistent. In short, the controls inherent in a competitive, knowledgeable free market system do not appear to operate, and it is little wonder that the FTC might see it as within its mission to try to correct this situation. And indeed this seems to be the case. The approach has been to concentrate on restrictions on advertising of health products and services (prescription drugs, physicians' services, eye glasses and the like); alleged price fixing (relative value studies, for example); health manpower practices (including accreditation of medical schools); restrictions on the scope of practice of allied professionals; competitive restrictions (including acts or practices that allegedly inhibit development of health maintenance organizations or other alternatives to the fee for service model); and deceptive advertising (including a recent action against egg producers who made a deceptive health claim). From present indications FTC activity in the field of health seems likely not only

to continue, but probably will increase and be buttressed by actions from the Antitrust Division of the Department of Justice.

So once again it appears that medicine and health become the crucible in which social policy for the future is formed. It is easy enough to dismiss all of this simply as harassment, as one more undeserved and malicious attack upon medicine, or as a further expression of antiprofessionalism and anti-intellectualism in our egalitarian society—or even as a federal agency simply doing what it was created to do. But it is more than these. It is yet another rather simplistic approach to solving the problem of the rising cost of health care, and another one based on a false assumption—the assumption this time apparently being that the cost can be controlled if health care is considered as a simple trade and if the rules of the marketplace are imposed upon it. This assumption is apparently made in the face of a substantial amount of evidence that the rules of the marketplace are inappropriate and ill-fitted to the problems of health care, and simply do not work in this area. But beyond this, the FTC approach to health will have profound technologic and social consequences if it is pursued to its conclusion. If the apparatus by which the professions perform their special role in their special disciplines is destroyed, the professions themselves will become impotent and unable to meet the needs for special knowledge and skills which are utterly essential for the smooth working of an increasingly complex technological society. So far as is known there has been no thought given to this outcome, nor has there been any discussion of it. In medicine the FTC approach would return quality control of medical education and patient care to the marketplace, which is precisely where it was before 1910, when there were no professional standards or controls on medical education or patient care.

One can only conclude that this is likely to be a significantly retrogressive step in the further evolution of American medicine and of the American dream. But whether retrogressive or not, it is even more disturbing that a step which is likely to have such profound societal consequences should have been decided upon in the relative secrecy of an independent federal agency with no apparent consultation or discussion with anyone concerning the possible consequences of its actions. But be this as it may, what then is the recourse? The dollar costs of opposing actions of the FTC can be very great and it is already clear that they are beyond the means of many professional organizations who consequently have had no alternative but to capitulate. Perhaps the FTC staff and the commissioners themselves can become better informed of the likely social consequences of dismantling the professions of this nation in today's complex technological world. And perhaps, best of all, this important policy issue can and should be taken to Congress where it should probably have been decided in the first place. It is not yet too late and we urge that this be done soon. This is a civic responsibility in the interest of the citizens of the nation.

—MSMW

Infectious Mononucleosis

Self-Limited Lymphoproliferation

MONONUCLEOSIS SYNDROMES comprise a multitude of diseases characterized by the proliferation of abnormal mononuclear cells recognized in the blood. Three common examples, discussed elsewhere in this issue, are: infectious mononucleosis (IM), cytomegalovirus (CMV) mononucleosis and toxoplasmosis. Also included in this group are a number of other illnesses—rubella, adenovirus infection, infectious hepatitis and many other viral disorders. However, of all these diseases infectious mononucleosis has received the most intense clinical and laboratory investigation during the past ten years. These efforts have not been without success, in fact, the Epstein-Barr virus (EBV) has been identified as the likely cause of IM, the disease which Dameshek first called "a self-limiting leukemia."[1]

In the outstanding review in the Medical Progress section of this issue Fiala and co-workers have exhaustively compared and contrasted classical infectious mononucleosis with the related diseases, cytomegalovirus mononucleosis and toxoplasmosis. Although these three disorders have many common clinical features the authors describe characteristic differences in their clinical courses, epidemiologies and, particularly, laboratory findings. Of these three, only IM is associated with heterophil antibody as well as a large array of other anti-

EBV tests which are available for diagnosis of occasional patients with puzzling manifestations. Actually, CMV mononucleosis and toxoplasmosis are usually readily differentiated from heterophil positive IM by appropriate clinical, microbial and immunologic observations.

The genesis of heterophil antibody, a hallmark of IM, remains one of the interesting unresolved puzzles in this common disease. Heterophil antibodies were first described by Forssman[2] in 1911. Paul and Bunnell[3] subsequently noted their presence in four persons with IM, a disease which had been clearly differentiated from its British cousin, glandular fever, by Sprunt and Evans in 1920.[4] Davidsohn and Walker's[5] landmark discovery that the heterophil antibody of IM differed from the Forssman antibody of serum sickness provided the cornerstone of clinical laboratory diagnosis of IM. That the hetrophil antigen itself is not the cause of IM was shown by Leikola and Aho, who observed typical heterophil antibody responses in the absence of infectious mononucleosis (IM) in a group of volunteers immunized with cells containing the heterophil antigen.[6] Even though heterophil antibody may be an epiphenomenon in IM, its presence is a highly specific and sensitive finding. Fiala and co-workers have correctly pointed out the very low incidence of false negative and positive results for this test.

Clearly, the most exciting recent discovery in the disease is its relationship to the Epstein-Barr virus. Paradoxically, this probable viral cause of IM has provoked new questions regarding EBV's role as a human tumor virus. The discovery that EBV was causally related to IM was made serendipitously in 1967 by the Henles,[7] who were able to establish a continuous lymphoid cell line from the blood of a person only after she contacted IM. Since then virtually all long-term human lymphoblastoid cell lines have been shown to be infected with EBV. Furthermore, the considerable body of seroepidemiologic and virologic evidence compiled in the last ten years leaves little doubt that IM is the result of EBV infection.[8]

Perhaps the most intriguing mystery of EBV's relationship to IM is why the disease is, in fact, self-limiting. Under different circumstances, EBV infections have been causally linked to nasopharyngeal carcinoma and Burkitt lymphoma. A number of possible explanations of this spectrum of responses to EBV infection comes to mind. First, genetic differences in the immune response to many antigens are now recognized and the association of transplantation antigens and disease is well documented. However, no clear-cut genetic predisposition correlating EBV with its associated diseases has been shown to exist. Second, EBV infects B-lymphocytes and in IM there is an intense concomitant proliferation of T-cells presumably in response to the infected B-lymphocytes. Failure of the T-cell population to effectively control the infection might lead to unrestricted B-cell proliferation and eventually a tumor. Finally, socioeconomic, geographical and many other environmental factors are intimately involved in the outcome of EBV infections, especially in view of the high correlation of African Burkitt lymphoma, EBV and endemic malaria. In my opinion, the definitive proof of the existence of human tumor virus may emerge from unraveling the mystery of the subtle host-virus interplay responsible for limited lymphoproliferation in IM.

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Management of Patients with Aortic Valve Disease

FOR PROPER MANAGEMENT of patients with aortic valve disease, physicians should have knowledge of current information concerning the structural and functional changes that occur in the heart as a consequence of the pressure and volume overload states from aortic valve disease, the relationship of these changes to clinical findings and to prognosis, and the effects of surgical therapy for aortic valve disease. For a number of years, there have been methods available for evaluating the severity of the mechanical defects of aortic valve stenosis and insufficiency.[1,2] More

recently, methods have become available for evaluating the extent of left ventricular hypertrophy, dilatation and myocardial performance in the presence of aortic valve disease.[3] From studies in experimental animals and in man, it is clear that the left ventricular response to a chronic pressure overload, as occurs in aortic valve stenosis, is ventricular hypertrophy with an increase of wall thickness, while chamber volume remains essentially normal. The increase of diastolic pressure which is often observed in patients with aortic stenosis appears related to the increased wall thickness rather than to altered stiffness of the myocardium per se.[4] These conclusions are based on studies of ventricular wall stress during diastole or of the normalized force within the wall which is acting to increase wall dimensions with ventricular diastolic filling. The response to a chronic ventricular volume overload, as occurs with aortic valve insufficiency, is both ventricular dilatation and hypertrophy with a modest increase of wall thickness. It is of interest that ventricular hypertrophy is usually more pronounced in aortic valve insufficiency than in aortic stenosis.[5] On the basis of more recent studies, systolic performance of the hypertrophied ventricle appears to be normal, at least in the early compensated phases of adjustment to the chronic pressure and volume overload states.[6] However, the long-term effect of the mechanical overload from chronic aortic valve disease, as seen in man, is a depression of myocardial performance. The biochemical and ultrastructural changes that account for this reduced performance are not currently understood. The depressed performance is associated with further dilatation, hypertrophy and often myocardial fibrosis, and is accompanied by a reduced systolic ejection fraction and a reduced normalized velocity of circumference of fiber change, or Vcf. Recent studies show that patients with depressed ventricular performance, as evidenced by cardiomegaly, left ventricular dilatation and a low ejection fraction, have a reduced prognosis for survival, with or without surgical replacement of the aortic valve.[7,8]

In managing a patient with aortic valve disease, it seems important to recommend surgical intervention before the development of depressed myocardial function. There is evidence that following aortic valve replacement there is, in many patients, regression of both ventricular dilatation and hypertrophy, although values may not completely regress to normal.[9,10] Other studies indicate that this regression of ventricular dilatation and hypertrophy does not occur, or is minimal, in patients with aortic valve insufficiency that is associated with depressed myocardial performance.[11] Methods for clinical evaluation and for determining when heart catheterization and surgical operation should be recommended are described in some detail in the informative symposium, "The Medical and Surgical Management of Patients with Aortic Valve Disease" which is published in this issue. The diagnostic studies are directed toward evaluation of the mechanical severity of the aortic valve disease, myocardial performance and complicating lesions of other valves, and for the detection of significant coronary artery disease. Aortic valve surgical therapy may be indicated on the basis of the severity of the aortic stenosis or insufficiency, or because of the development of depressed myocardial function combined with a significant mechanical defect from the aortic valve disease. In other patients, operation may not be indicated because the mechanical defect is trivial and depressed myocardial function is severe; however, the minimal severities of aortic stenosis or insufficiency and levels of depressed ventricular performance for such decisions have not been precisely defined.

I have some minor disagreements and additional suggestions for evaluation of patients from those given in the symposium. I have not found that the left ventricular ejection time (LVET) is particularly helpful in evaluating the severity of aortic stenosis and I question whether this determination is worth the time and expense. The LVET is difficult to measure in aortic stenosis and there are too many factors other than the severity of the aortic stenosis that may alter the LVET. In addition, the LVET is not helpful in evaluating the severity of aortic stenosis in the presence of mixed stenosis and insufficiency, which is so often present. If there is a problem in evaluating the location and significance of heart murmurs, we have found that the new noninvasive technique of Doppler echocardiography is often helpful in addition to standard M-mode echocardiography.[12] If there are questions regarding the severity of aortic stenosis, whether heart catheterization is indicated or to what extent physical activity should be limited, a carefully carried out maximal treadmill stress test with frequent monitoring of arterial blood pressure can be helpful. Exertional hypotension is a frequent early finding in patients with hemodynamically significant aortic stenosis.

The spectacular advances in cardiac surgical operation for aortic valve replacement and in the outlook and prognosis of patients with aortic valve replacement are reviewed by Dr. Daily in the symposium referred to above. For patients with aortic valve disease to derive the maximum benefit from these advances, appropriate evaluation and recommendation for operation are important. With the current low risk of operation for elective valve replacement, improved surgical techniques to minimize myocardial damage at the time of open heart surgical procedures and the improved function, durability and risk of complications of prosthetic and tissue valves, a more aggressive approach to earlier operation in a patient with hemodynamically significant aortic valve insufficiency might well be justified.

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Medicine and the Quality of Life

Refer to: Watts MSM: Medicine and the quality of life—A report of a forum. West J Med 126:499-504, Jun 1977

Report of a Forum

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THE QUALITY OF LIFE seems to be emerging as a national concern, perhaps a national purpose. It is increasingly cited as a goal of medicine and health care by government spokesmen and various opinion leaders, and appears with increasing frequency as a term used in the national dialogue. There are evident expectations by many that medicine can improve the quality of life and that this goal is related somehow to access to a high quality of health care. But in none of this dialogue or discussion is it yet clear just what is meant by quality of life or just how medicine and health care can bring about its improvement. There is need for some better description and means of measurement of this elusive and fascinating concept, particularly if it is something to strive for as a national goal.

It is clear that many factors enter into the quality of life for any person. Some of these factors are endowed at birth, some seem to be acquired or lost through interactions with environmental forces, and others seem to pertain to purposeful actions by the person. One's genetic and cultural heritage is endowed. The importance of a healthful and pleasing environment, and the growing social, economic, political, and even physical interdependence of humans with each other and the environment can easily be recognized. Also evident is the perhaps overriding significance of personal fulfillment, or fulfillment of one's individual potential. And yet another dimension quickly becomes apparent. It is the dimension of time for the human species on this planet. Not only is there a now, but there is a continuum of past, present and future which bears directly upon health, well-being and quality of life for humanity. We have a heritage from the past, we have the difficult problems of the present and we have an obvious capability to influence the future; the importance of each of these is only just beginning to be perceived.

This report is largely a summary or distillate of a forum conducted in THE WESTERN JOURNAL OF MEDICINE in the latter half of 1976 and extending into 1977. The forum began with the publication of several statements by distinguished contributors to thought on this subject, and then continued with other comments submitted by readers for publication in the forum. In this report an attempt is made to take this material, and information from other sources, and to fashion a broadly based statement on the subject of medicine and quality of life which can then be a point of departure for further discussion in these columns and elsewhere.

A Personal Matter

Happiness

Stripped of its trappings, quality of life emerges as a deeply personal matter. It really exists only in terms of the person. Personal happiness quickly comes to mind as being important. Even the determinants of happiness differ from person to person, from social group to social group, and from time to time. To some extent happiness is biologically determined by the genetic code to produce simple joie de vivre. Joy of living relates to our biochemistry and to our nature. A sufficiency or even a surfeit of material wealth is not enough to assure joie de vivre or even happiness. Food in the belly alone, at one end of the spectrum, or a plethora of material goods at the other, will not alone assure either happiness or quality of life. Something more seems to be needed, something emotional, something a person cares deeply about—a thing, a person, a cause. And curiously this something need not be attained or even attainable, it need not even be worthwhile in a social sense, but it must have an emotional importance to the person. Its opposite is apathy, boredom, ennui and depression—surely not happiness and surely not quality of life.

Purposes

Many who have pondered the subject suggest that quality of life may be more closely related to individual purposes than to anything else. It is these purposes, and the freedom to attempt their achievement, that gives rise to a person's aspirations and expectations, and thus to the context in which a person judges happiness or the quality of his or her life. Purposes reflect self-interests, the interests of others, community interests and perhaps even a "collective subconscious." It was suggested in the forum that the ability to formulate and implement purposes is therefore probably essential to achieving quality in a human life experience.

Social Influences

There are also important social influences in this very personal matter of quality of life. The social and political systems into which we are born and in which we live influence what we believe to be quality in our lives and our purposes. For example, the changing status of women is clearly changing the purposes of a large segment of society with all that this implies for each person and for society as a whole. The new emphasis on conservation of resources and on social rather than economic gain surely influence both the purposes and the quality of life of many people in many ways. Perhaps some of these values are in some fashion mediated through the "collective subconscious"—if there is such a thing. In any case there are collective purposes that influence individual purposes and behavior. The American drive for progress, and particularly the drive for material progress, which has brought this nation to its present state of relative affluence, is such a social or political purpose, as is the collective purpose expressed in the words "we shall overcome." And here again there can be the obverse—the hopelessness and purposelessness which pervade some geriatric nursing homes, for example. There seems to be something contagious about purposes, or purposelessness for that matter. They tend often to spread from person to person and this too can affect aspirations, expectations and quality of life .

It was noted that attractive and even noble social purposes can have bad as well as good effects on quality of life. For example, the growing emphasis on the rights and needs of the individual person, which is attractive and even noble in conception, has in its practice led to an unanticipated increase in crime, muggings in the streets and wanton violence. It was pointed out that this shift in emphasis from a person being responsible to adjust to society, to society as a whole feeling a responsibility to adjust to the rights and needs of individual persons may not be entirely a good thing for either. Social influences during early development are also being shown to influence individual responses to recurring life stresses. It has been found that persons who are deprived in various ways during the early developmental periods of infancy and childhood may respond to stresses in later life with demoralization, depression and helplessness, with obviously undesirable effects upon the quality of their lives. It seems clear enough that there is a real relationship between the social and even political environment in which a person is born and lives and the quality of life, but it is not a simple relationship, and the ramifications are as yet poorly understood.

Human Nature

Human history and the long experience of trial and error in human cultures also provide insights into human nature and its relationship to quality of life for human beings. The axioms of history tell us that work, respect, self-confidence, personal responsibility for one's self, community responsibility for one another, a sense of belonging, an opportunity to exploit one's ingenuity, and the prevention or assuagement of fear are also very important influences on the quality of a person's life. And there are no doubt many other such biological, psychological and social forces that bear upon human nature and that also must be taken into consideration in any description or definition of what is meant by quality of life.

What Can Physicians Do?

Some will say that none of this is the proper concern of medicine, that these are problems for the individual person and for society to work out, and that a physician should become involved only when a person can no longer cope and turns to a physician for help. In a sense this is true. There is no way medicine can be responsible for or solve all of the personal or collective social problems that must be solved to achieve quality of life. But a physician does seem to have some responsibility beyond simply relieving the symptoms of stress or treating an illness or injury.

Sensitive and experienced doctors have always considered the problems of the whole patient—or to put it another way, the problems of the patient as a whole—and have tried to help show the way to solve them as a means of improving health and presumably quality of life. This responsibility has found expression in the historic role of the physician: *docere*—to teach. Doctors of medicine are particularly well fitted for this role. Situated at the interface of personal health and unhealth, physicians are well informed about human biology and its disorders, have an unusually close experience with human nature seen both at its best and at its worst, and are able to assess the impact of social and environmental forces upon a patient who is also a person. It is suggested that physicians and the medical profession do have a role, and that their role is to use their special knowledge and experience to teach. More specifically, it is to teach persons how to deal with their problems and thereby achieve a better quality in their lives, as well as to teach what must be done to maintain health, and to prevent disease, disability and untimely death.

Health and Quality of Life

Is Health Necessary?

Although it is often assumed that good health is basic to quality of life it was repeatedly noted in the forum that good health is by no means essential. In fact quality of life can be achieved in the presence of illness. A disabling pain or a serious handicap may challenge a person to accomplish some goal that gives a life the purpose and meaning so necessary for its quality. Even in a chronic illness, such as end-stage renal disease, it has been shown that quality of life is possible. It depends upon the patient taking an active part and participating as a full partner in the care and in the management of the illness, and in this way maintaining the personal sovereignty that is a sine qua non for quality of life.

Health itself is not easily defined either in the context of chronic disability or of quality of life. In many ways it appears to be a highly subjective concept. The definition can depend upon what a person wants to be able to do. It can relate to one's occupation. An athlete certainly has one idea of the meaning of health and a scholarly recluse quite another. The criteria for health also vary with the times. For example, some years ago plumpness or even obesity was thought to mean health and now leanness is the popular standard. And it is curious that throughout history, and even today, health is far less interesting as a topic of general conversation than disease and its symptoms and treatment.

It is probably true that health is really not necessary for quality of life. But while it may not be essential, health is nevertheless important, and in later years it may almost entirely determine whether or not quality of life is even possible for a person.

Beliefs About Health

Much of the current conventional rhetoric suggests that health equals the absence of disease, that the best way to improve health is through medical care, that scientific medicine is precise and that most problems of health and disease should be amenable to technical solutions. The success of medicine has been measured by objective remission of illness, repair of injury or the temporal survival of a patient. It has been inconceivable to many that anyone could ever place such values as security, money, work or pleasure in a higher personal priority than health. Beliefs such as these are very widely held and have largely determined medical as well as legislative efforts. There has been relatively little attention given to the effect of medical ministrations, or legal ones for that matter, on the quality of life of afflicted or affected persons. These kinds of beliefs, which are based on a number of incorrect assumptions, have understandably led to much disillusionment. Questions are now being raised about the aggregate effect of much more extension of life expectancy or freedom from disease upon the quality of the lives so extended. For example, how much is really accomplished by the aggressively successful antibiotic treatment of pneumonia in a senile patient in a rest home? It is even being said that there may be too much rather than too little medical care. In any case there is dissatisfaction that the quality of life of ill persons has been so little improved even when medicine has prolonged many lives and cured many illnesses.

Environmental Quality and Health

The quality of the environment clearly may affect a person's health, and quality of life as well. Again, other personal, social or economic values may be given priority over a healthful environment. Persons who cap oil gushers, choose to live and work among the poor in ghettos, or

labor in coal mines may sacrifice a healthful environment to other values which for them have a higher priority. The kind and quality of the public health and the social support systems available also contribute importantly to environmental quality and to health. Carcinogenic agents in the environment; the effects of stressful living; dietary habits that may lead to the development of disease; and pollution of air, land and water resources can all obviously affect health and quality of life in many ways. We are only beginning to sense their importance.

Behavior and Health

From what has been said it appears that further advances in health, and quality of life to the extent it depends on health, will result more from changes in personal behavior than from any scientific discoveries that are likely to occur. Once again we return to the premise that quality in one's life depends more upon one's purposes and how one sets about to achieve them than upon almost anything else. It was pointed out in the forum that the army represents an ideal health maintenance organization. The health of personnel is of high priority, and there is substantial control of both environment and behavior. But when soldiers are off duty, the army has less control, and this may be part of the reason that there seems to be no significant difference between the incidence of illness and injuries among comparable groups in or out of military service. Human behavior among free and independent people is not easily standardized for health or any other purpose. But no doubt society will keep on trying.

What Can Physicians Do?

Good health arises from factors over which physicians have far less control than is generally thought. Life styles, social conditions, economic status, environmental factors, and good and bad purposes are all essential ingredients. Physicians can and should play a major role in defining health, but in the final analysis it is society that defines quality of life and adapts the medical system to this conception and definition. However, physicians can and should contribute their expert advice based upon their scientific and experiential expertise with human biology, human nature and well-being. Medicine also can provide the resources and information to help persons make informed decisions concerning their health and quality of life, and this is important.

Health Care and Quality of Life

Expectations of Medicine

The forum suggests there is a growing tendency to assume that the medical profession can help individual patients and the community as a whole to achieve a higher quality of life. For instance the black community appears to view medicine as primarily concerned with improving quality of life. Practitioners of medicine are expected to improve the entire community. The poor expect employment and economic benefit from the health field. Medicine is called upon to relieve total life situations. In isolated rural areas a doctor or a health facility gives a sense of security. For many it seems to be an article of faith that medicine will be a primary avenue toward improving quality of life for all mankind—an expectation that medicine may not be able to fulfill. In fact it was said that doctors have probably contributed more and failed more to improve the quality of life than any other profession.

Impact of Health Care

Medicine has done and is doing much to improve quality of life. The scourge of infections has been largely controlled. Accomplishments in surgery, anesthesiology and postoperative care have been spectacular. Advances in diagnostic radiology and laboratory technology have been equally important and equally costly, though perhaps not quite so spectacular. Mental illness has been made far more manageable and there have been great improvements in emergency care. And not to be forgotten is the crucial function of caring —providing the sympathy and reassurance that only physicians can provide. The fear of illness has been reduced and the threat of disability softened. All this has helped enhance quality of life for many. And there will be further improvements.

But there have been negative factors. The costs of being ill have risen alarmingly. There is a significant and growing amount of iatrogenic disease. More sophisticated laboratory tests have produced more false positive findings, with the attendant unnecessary worry and costs. A drug-dependent society seems to have come into being. And dying is often expensively and sometimes heartlessly prolonged. There are other prices to be paid for these medical advances. There is need to support an enlarging elderly population with its accompanying chronic disease and disability. We have developed unrealistic expectations of doctors as evidenced by the present epidemic of

malpractice suits against physicians and hospitals. Unrealistic assumptions and expectations go even further when some say that if there were no poverty, no racial prejudice and no male chauvinism there would be no mental illness. And it has been asked if doctors would contribute more by doing less, and this is worth pondering.

We can assume that progress in biomedical research will continue and that there will be new knowledge in the future. For instance, recent research in recombinant DNA has introduced profound new conceptual implications which can affect many aspects of subsequent life, including its quality, in as yet unpredictable ways. But all of this discussion of the positive and negative impact of contemporary medicine tends to overshadow the basic fact that all medical decisions involve value judgments as well as clinical science and the fact that certain assumptions upon which our concepts of health and health care are based may be faulty. The illusion of cure appears to be the central clinical problem in dissatisfaction with medicine's contribution to quality of life.

Emerging Role of the Patient

A significant and apparently new observation in the forum was that as the health care delivery system grows and becomes a more powerful political structure it tends to alienate both physicians and patients. It reduces patients to virtual mendicancy and limits both the freedom and responsibility of physicians because options within this health care delivery system are determined by society. Freedom for both physicians and patients consequently becomes impaired and also inextricably linked. It was suggested that physicians should foster greater independence for patients ("patient dependence is a trap") because otherwise the freedom of both surely will be lost. Patients should be educated to be responsible for their own health and continuity of care, and to become true partners in the therapeutic team. But there is a subtle point involved. Physicians still have a particularly professional obligation to their patients—the role of physician-parent and professional advisor cannot be completely abrogated. This essential function must be carefully balanced with a genuine respect for the dignity and integrity of a free, properly informed human being who is a patient.

What Can Physicians Do?

It was suggested that the primary duty of the medical profession is the prevention of disease and injury and the restoration of health or tolerable physical and mental well-being. A physician should always see the patient as an anxious concerned person who can be restored to useful enjoyable life by taking into consideration emotional, economic and family factors. The patient should be a full partner in a "team" approach. It was suggested that this can improve quality of life for the person, the physician and the community as a whole.

It was further suggested that it is the obligation of physicians to make full disclosure to a patient, measured to the intellectual and emotional capacity of the patient, and that there be forthright recommendations. But a physician should always respect the judgment of a patient who, for whatever reason, still elects to place priority on something other than health or longevity or even freedom from discomfort.

But the forum seems to go further in suggesting that physicians should begin to encourage patient independence. By doing this, medicine can support individual purposefulness and personal quality of life, and at the same time enhance the freedom and responsibility of both patient and physician, which seem likely to be essential for the future quality of patient care.

Some Dilemmas and Directions for Medicine

Medicine in Today's Culture

There is reason to believe that some significant changes may be occurring in the place of physicians in today's culture in America. For example, many primary care functions are being assumed by other health professionals. Many secondary and tertiary care physicians are becoming specialized technicians. The outcomes of treatment are admitted often to depend as much upon the patient as upon the physician. The outcomes of prevention are seen to depend as much upon the understanding and cooperation of the public or the consumer as upon the ministrations of a doctor, and the achievement of quality of life is becoming recognized to depend very much upon the individual person. Furthermore, many patients and many consumers now seem to be listening to a different drummer. The concept of the "consumer" rides high and its adherents expect to consume, to receive, to be fed as it were; the consumer movement seems to feel little responsibility except to see that consumers are taken care of. Medicine itself appears to be losing something of its traditional role. It is being weakened not only

by other professions taking over its duties, but by its own too-frequent failure to care for the whole person; this failure seems to have led to a growing acceptance by the public of alternative approaches to patient care. Medicine has not identified a new role nor has it yet dealt successfully with these developments—nor has the medical point of view been successfully brought to bear to influence the culture. Rather, society appears to be shaping the place of physicians, and the medical point is too frequently not heard or is simply ignored.

Should There Be Some New Approaches?

Medicine may relieve suffering and correct reversible illness. Medicine provides a framework for understanding the effect of environmental factors on health and healthful living. Through education and public health, medicine can improve some aspects of the environment and to some extent influence the functioning of society and the vitality of its institutions. Biomedical research contributes to our understanding of reality and to our capability for self-determination. And very significantly, medicine is an anthropologically important ritual of social expression which commits physicians to coming to grips with the human condition. While in theory the role of medicine may be only to prevent or correct disorders of the body and the mind, in practice this role extends to many other aspects of life—and to quality of life. A physician is expected to be a general counselor as well as a healer. Perhaps some new approaches are now needed.

Indeed the forum suggested that medicine now eschew taking bows for past contributions, that it abandon its heritage of myths, and begin to apply its unique background of biological knowledge and human experience more realistically and more directly to the problems of the day. It might question more aggressively the technologic imperative, the imperative that drives practitioners to intervene simply because they can and not because they should. It might begin to address more explicitly some of the questions involved with human purposefulness—the human purposefulness that seems so integral a part of quality of life—and the relationship of this to what should be the aims of patient care. For example, should the aim of patient care be to restore a condition of freedom and maximum capability to attain the purposes of medicine and health care, or, to put it another way, to what extent may health or quality of life be compromised by the purposes medicine promotes? Then should or should not medicine become a militant advocate of what its knowledge and experience lead it to believe are the "right" purposes? And it was suggested that medicine might begin by erecting a more efficient, more effective and more equitable system of health care, or play a more central and aggressive role in doing what needs to be done to accomplish this.

This all suggests that medicine should begin to assume a more aggressive posture and extend its own purposes beyond the care of the sick, that it begin to promote greater freedom for patients including more personal responsibility and more attention to self care, and that it become an advisor, counselor and advocate to teach health education to patients and to the public. The forum even went beyond this, suggesting that physicians use their special knowledge and experience in health and its disorders to act as informed citizens stimulating change in public attitudes about issues, becoming involved and taking stands, recognizing and defining those things in society that have a beneficial or deleterious effect on health and quality of life, and mobilizing citizen pressure to strengthen what should be strengthened and to change what should be changed. The place of the physicians in society is shaped by the culture. Conversely, the medical point of view can influence the culture. It seemed to be suggested that more of the latter is now needed.

Conclusion

The quality of life issue is a seminal one for the medical profession. It brings into question the whole current concept of health care and even of disease itself. Its resolution will determine not only the future direction of health care and the health care system, but the role, and even the freedom, of physicians themselves. Quality of life cannot be given or provided. In the final analysis it is a very personal matter closely related to personal purposes. While medicine cannot by itself determine or even define quality of life, it can help patients and the public to achieve it through better personal health and a more healthful environment, and by helping to create the circumstances in which a person can achieve a better personal quality of life. On a broader scale, it can also help society itself to create a milieu in which a greater number of citizens can succeed in achieving more quality in their personal lives. The forum offered many suggestions for what might be done and how it might be done.

CASE REPORTS

Refer to: Santiago SM Jr, Klaustermeyer WB, Brockman G: Pulmonary thromboembolism in erythema multiforme. West J Med 126:505-506, Jun 1977

Pulmonary Thromboembolism in Erythema Multiforme

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ERYTHEMA MULTIFORME is an acute inflammatory disease with an extremely wide range of clinical presentation. Signs may vary from a few scattered lesions of the skin and mucous membranes to a generalized bullous eruption with severe systemic manifestations.[1] The disease is commonly associated with a number of unrelated conditions. These include bacterial, viral, mycoplasmal, protozoan and mycotic infections; drug reactions; vaccination; contact dermatitis; collagen vascular disease; radiation therapy; internal malignancy, and hormonal changes during pregnancy and menstruation.[2,3] In addition to the cutaneous features of erythema multiforme, there may also be involvement of the respiratory tract, heart, kidneys, gastrointestinal tract and central nervous system.[3] Pulmonary manifestations include tracheobronchitis, pneumonitis, pulmonary consolidation, pleural effusion and hilar adenopathy.[1,4-8] In the following report the case of a patient with recurrent erythema multiforme and pulmonary thromboembolism is described.

Report of a Case

A 29-year-old black man had a history of recurrent episodes of erythema multiforme since 1964 requiring high-dose corticosteroid therapy and frequent admissions to hospital. A typical episode consisted of a maculopapular and vesicular eruption involving the skin of the extremities and mucous membranes of the oral cavity and glans penis accompanied by difficulty in speaking and swallowing. Numerous efforts to identify specific etiologic factors have been nonproductive.

In September 1973 a recurrence of erythema multiforme was accompanied by severe right-sided pleuritic chest pain, shortness of breath and a nonproductive cough. Diminished breath sounds were noted at the right base and a right-sided pleural effusion was seen on roentgenograms of the chest. Thoracentesis yielded a minimal amount of serosanguinous fluid that was sterile on culture. The patient refused further diagnostic studies and gradually improved over a period of several weeks.

The patient was readmitted on February 26, 1976, to the Wadsworth Veterans Administration Hospital in Los Angeles with a five-day history of right-sided pleuritic chest pain, shortness of breath and an acute exacerbation of erythema multiforme. On physical examination, temperature was 38.3°C (101°F); pulse rate, 104 beats per minute; respiratory rate, 22 per minute, and blood pressure, 110/90 mm of mercury. Vesicles and erosions were noted on the lips, buccal mucosa, tongue, hands and feet. Increased fremitus in the right mid-posterior portion of the chest and accentuation of the second pulmonic heart sound were noted on auscultation. Laboratory findings included a hemoglobin level of 14 grams per 100 ml, leukocyte count of 13,300 cells per cu mm and no abnormalities on an SMA-12 (Sequential Multiple Analysis). Arterial blood gas studies done on admission showed an oxygen pressure of 76 mm of mercury, a carbon dioxide pressure of 35 mm of mercury and a pH of 7.43. An infiltrate was noted in the right mid-lung field on roentgenograms of the chest and a perfusion lung scan with technetium Tc 99m-labeled macroaggregated albumin (99^{m}Tc-MAA) showed perfusion defects in the right upper and lower lobes and lingula. On pulmonary angiograms a filling defect was noted in the right main pulmonary artery with absence of flow to the right upper lobe (Figure 1). The patient was treated with heparin and maintenance prednisone (40 mg per day) was continued. Clini-

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Figure 1.—Pulmonary angiogram showing filling defect in right main pulmonary artery and absence of flow to the right upper lobe.

cal improvement occurred in two days with reduction of the fever and chest pain. Radionuclide venograms (using 99^{m}Tc-MAA) of the lower extremities done a week after admission were normal. The skin and mucous membrane lesions gradually resolved and the patient was discharged on a regimen of sodium warfarin (Coumadin®) and prednisone after two weeks in hospital.

Discussion

The precise pathogenesis of erythema multiforme has not been firmly established. Its occurrence after exposure to a variety of unrelated agents may suggest an immune mechanism and histopathologic findings of allergic vasculitis would tend to support this.[9] Vasculitis may account for some of the reported manifestations of erythema multiforme including glomerulonephritis and microangiopathic hemolytic anemia.[10,11] The pulmonary vascular occlusion in our patient may likewise be a manifestation of the vasculitis of erythema multiforme. He had one documented episode of pulmonary thromboembolism that occurred coincidentally with an exacerbation of erythema multiforme. A previous bout of acute erythema multiforme in September 1973 was also accompanied by features suggestive of pulmonary thromboembolism (pleuritic chest pain, dyspnea and serosanguinous pleural effusion). To our knowledge, pulmonary thromboembolism has not been reported in erythema multiforme. It is possible that some of the previously reported cases of "pneumonitis" in erythema multiforme are secondary to pulmonary thromboembolic disease.

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Refer to: Seltzer RA: Pneumoperitoneum following intermittent positive pressure breathing. West J Med 126:506-509, Jun 1977

Pneumoperitoneum Following Intermittent Positive Pressure Breathing

RONALD A. SELTZER, MD
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THERE ARE SEVERAL reports of pneumoperitoneum secondary to progressive pneumomediastinum in neonates with respiratory distress syndrome or chronic pulmonary disease.[1-4] Recently, this phenomenon has been described in three adults receiving mechanical ventilation, in two of whom exploratory laparotomy was done for suspected perforated viscus.[5] The following report is the

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Submitted July 21, 1976.

Reprint requests to: Ronald Seltzer, MD, Department of Radiology, Sequoia Hospital, Redwood City, CA 94062.

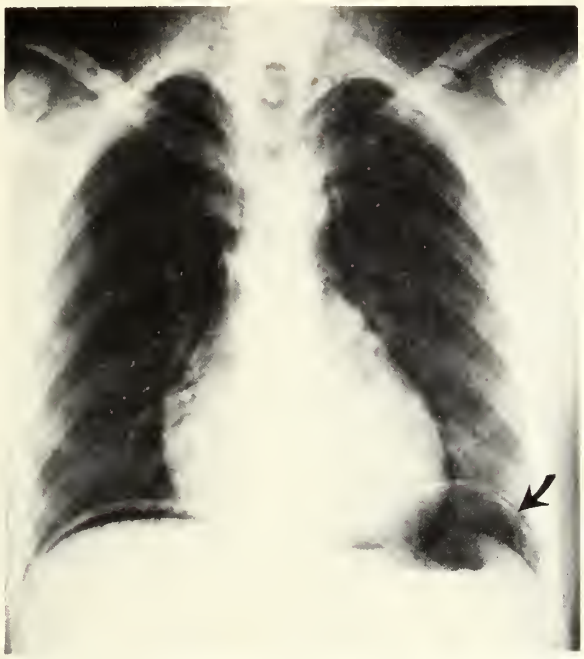

Figure 1.—Posteroanterior view of the chest on admission. Note subcutaneous and mediastinal emphysema and pneumoperitoneum. A small streak of air is seen in the retroperitoneal space along the inferior aspect of the left hemidiaphragm (**arrow**).

case of a young man with asthma in whom pneumomediastinum and pneumoperitoneum developed while the patient was using an intermittent positive pressure breathing (IPPB) machine at home.

Report of a Case

In a 22-year-old white man, low anterior chest pain occurred at home while he was using isoproterenol in an IPPB machine with the pressure limit at 20 cm of water. The patient had had chronic asthma since childhood and was maintained on a regimen of prednisone and aminophyllin taken each day. One month earlier, a small left pneumothorax had developed while the patient was using the same IPPB machine. It subsided with conservative therapy. On physical examination at the current admission, the abdomen was noted to be soft. Cervical subcutaneous emphysema was present.

A radiograph of the chest showed subcutaneous emphysema, pneumomediastinum, pneumoperitoneum and air in the retroperitoneal space (Figure 1). Results on a gastrografin upper gastrointestinal series were normal. The patient was treated conservatively with spontaneous reduction of the pneumomediastinum, subcutaneous

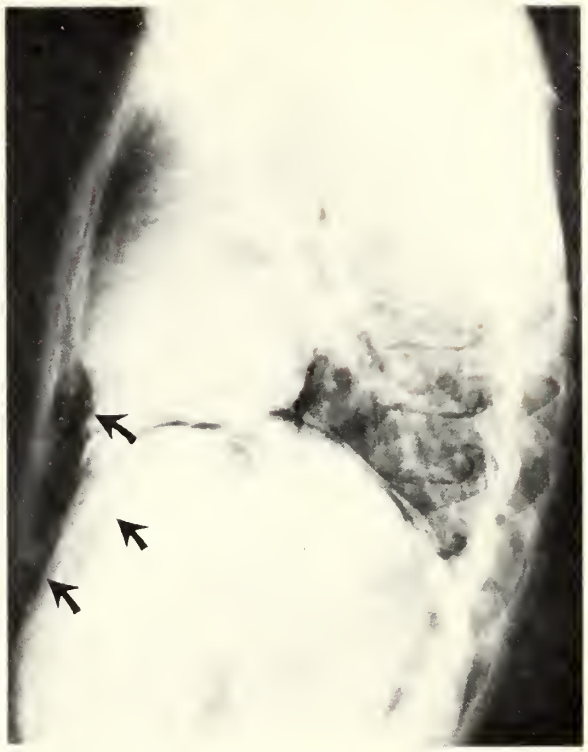

Figure 2.—Lateral view of chest during fourth episode. Note the extensive air descending from the anterior mediastinum into the anterior retroperitoneal space (**arrows**).

Figure 3.—Posteroanterior view of the chest during final admission. A small left pneumothorax has appeared and there is a large pneumoperitoneum. Little retroperitoneal air is seen.

emphysema and pneumoperitoneum over the next four days. He was cautioned not to use the IPPB machine again.

During the ensuing two months, the patient had three separate episodes of small left pneumothorax after coughing or sneezing and a fourth episode of spontaneous tension pneumothorax requiring tube drainage. These episodes were accompanied by varying degrees of pneumomediastinum, pneumoperitoneum and air in the abdominal wall, retroperitoneal space and neck (Figure 2 and 3).

Finally, two months after the initial illness and while in hospital because of another episode of pneumomediastinum, pneumothorax and pneumoperitoneum, the patient became pale and breathless, and appeared to be in shock. He died in fifteen minutes despite vigorous attempts at resuscitation. On autopsy, a saddle embolus in the main pulmonary artery was found. There were no abnormal communications between the chest and abdominal cavity, nor evidence of perforated viscus.

Discussion

Almost all of the previously reported cases of pneumoperitoneum following pneumomediastinum have occurred in patients receiving continuous mechanical ventilation, nearly always with intubation, and often with positive end-expiratory pressure.[1-8] There is a single reported case of spontaneous pneumomediastinum and pneumoperitoneum in an 18-year-old man during a severe attack of asthma[9] and another following a crushing chest injury.[8] It would seem that hyperinflation or high alveolar pressures, or both, are necessary to produce this phenomenon, although it has occurred rarely following tracheostomy[10] and after dental extraction.[11]

The current case is the first in which pneumoperitoneum occurred secondary to the use of oral IPPB. Although the patient stated that the pressure was set at the customary level (20 cm of water), there is no way of knowing if he was using the machine properly. Moreover, since the subsequent episodes occurred spontaneously, it is uncertain whether the initial event opened the necessary anatomical pathways or if the tissues were particularly susceptible to dissection by air.

The mechanism of development of pneumothorax, pneumomediastinum and pneumoperitoneum has been established experimentally and shown to occur in many different clinical settings.[12] Air under increased pressure within the alveoli ruptures into the interstitial space and dissects along the pulmonary vessels to the mediastinum. Continued leakage of air may produce subcutaneous emphysema as the air dissects along the fascial planes to the neck, pneumothorax if the air ruptures into the pleural space, or pneumoperitoneum as the air dissects inferiorly along the visceral and the vascular planes to the retroperitoneal space and then ruptures into the peritoneal cavity.

It is interesting that nearly all of the reported cases of pneumoperitoneum following pneumomediastinum of pulmonary origin have occurred in infants or in relatively young adults (in all reported cases the patients have been less than 49 years old). This distribution is probably a reflection of the relative resistance to the flow of air within the tissues, and may reflect the development of adhesions with aging or perhaps weakening of the parietal pleura in older persons. In the neonates in whom pneumoperitoneum developed, it is postulated that massive, tension pneumomediastinum allows the air to dissect posteriorly to the natural diaphragmatic openings and thence to the abdomen.[4] In the case reported here, the radiographs (Figure 2) suggest that the air dissected directly from the anterior mediastinum into the anterior chest wall and then into the retroperitoneal space of the anterior abdominal wall and finally into the peritoneal cavity, a pathway which has been described before.[10] The crescent shaped streak of the retroperitoneal subdiaphragmatic air which may be thickest at a point medial or lateral to the highest point of the diaphragm can be distinguished from intraperitoneal air which rises freely to the highest point of the diaphragm (Figure 1) and may, if fluid is present, have a flat lower margin.[10]

Other causes of spontaneous pneumoperitoneum unrelated to ruptured viscus or laparotomy are known. They include entry of air through the female reproductive tract during sexual activity, douching, pelvic examination and postpartum exercises, as well as pneumatosis cystoides intestinalis.[13] It is important to be aware of these possibilities in order to avoid unnecessary surgical operation in a search for a ruptured viscus. Such operations had been done in three of the reported cases that occurred following pneumomediastinum in adults.[5,8] Unnecessary laparotomy has also been done in an infant.[3] In the current case and in three others, gastrografin contrast studies were

used to search for a ruptured viscus.[1,2,8] Abdominal paracentesis has also been used to exclude peritonitis.[2,4,8]

Summary

A case is presented of pneumoperitoneum secondary to the use of an intermittent positive pressure breathing machine. Although uncommon, this potential source of pneumoperitoneum should be considered and, if indicated, additional diagnostic studies employed in order to avoid laparotomy to search for a ruptured viscus.

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Handling a Parent with Asthma

How can negative psychological effects of an asthmatic parent on a child with asthma be reduced?

The first thing I think I would do is say to the parent, "You know, it's just going to be very difficult for you to follow my advice, because you've got another set of advice in your head from when you were little, and I really would like to help you separate those things out." So you are as clear as possible about the fact that there's a problem. You've not judgmental about it; you're just describing that this is going to be difficult for them. Then you say, "OK, it would help me to learn as much about you and *your* asthma as possible." And then get them to tell you everything terrible they can think of about their own asthma and about their relationships with their parents, so that you've got a backlog of information to work with. Then, when you're advising the parent—let's say, for example, it is a mother who doesn't want to let her boy go out and play because every time he goes out and plays he comes back wheezing a little bit—you can say to her, "How was it with you when you were little?" And then say, ". . . it's really OK for him to go out and play . . . he has to learn his own limits. If you set limits, you're depriving him of learning . . . ." You simply try to get as specific as possible about your advice and the child's needs, and accept the parents' problems and help him or her to work with them. Most parents really appreciate that . . . they really don't mind that kind of constructive hassling.

—WILLIAM M. BOLMAN, MD, *Honolulu, Hawaii*

Extracted from *Audio-Digest Pediatrics*, Vol. 22, No. 4, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1577 East Chevy Chase Drive, Glendale, CA 91206.

Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgment before publication.

Miconazole

To the Editor: The recent exchange of correspondence on the subject of miconazole therapy (West J Med 126:315-317, Apr 1977) was informative, and while I do not wish to prolong it unnecessarily, there are some necessary corrections.

The statement that our initial report on meningitis[1] was "based upon" unpublished observations in one or two patients by Dr. Sung and co-workers is unfounded, since it was based on careful studies by several individuals in 13 of our own cases. The intrathecal dose used was not derived from extrapolation of commonly used doses of an unrelated drug, as the method now detailed by Sung, but from documentation of the pharmacokinetics and side effects of stepwise increments (beginning at 1 mg), to derive a tolerable dose that produced prolonged cerebrospinal fluid levels above the minimal inhibitory concentration of the organism. The results of these pharmacological studies are available elsewhere.[2] It is worthwhile to air this difference in approach for your readership, since I submit the latter method is preferable when confronting a new compound with unknown pharmacological properties, such as was the case with miconazole.

I omitted indicating that the percent incidence figures of side effects I cited, which Sung reports not observing in his 13 patients, were based on a denominator of data from 45 treatment courses.[3] These differences may depend in part on the frequency of determinations in individual cases.

Dr. Sung's clarification that he feels intrathecal therapy is necessary for patients with coccidioidal meningitis misses the point, since the four patients I cited who responded to intravenous therapy alone were from a subgroup of ten with coccidioidal disease.[1] References to statements by Dr. Winn are irrelevant here, since he was referring to an unrelated drug.

Finally, (1) the direct quotation, "early paper", to refer to our initial brief report as attributed to me does not appear anywhere in my preceding letter and (2) Sung does not indicate why it was deemed necessary to probe acceleration of the one-hour infusion time previously shown to be safe to the point of cardiotoxicity.

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Stanford University School of Medicine

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The Saccharin Affair

To the Editor: In regard to the Saccharin Affair: Indeed, there are some things that *are* best left to doctors, as suggested in your editorial comment in the April issue [Watts MSM: The Saccharin Affair (Editorial). West J Med 126:309, Apr 1977]. But there are also some things that are best left to those who have studied the relevant data.

You appear to be ready to accept that the Food and Drug Administration (FDA) reacted auto-

matically to "possible but as yet unproved dangers." You are in good company: At a dinner party shortly after the first saccharin announcement, I found a Nobel laureate in physics, a chancellor of a university, a distinguished attorney and their wives all accepting the published canard that the FDA acted on a single experiment in rats involving vast doses of saccharin. The fact is that the experiment cited was but one of several that strongly implicate saccharin as a cause of bladder cancers. If you had known this, would you have written the same editorial?

RODNEY R BEARD, MD
Head, Division of Preventive Medicine
Department of Family, Community and Preventive Medicine
Stanford University School of Medicine

In answer to Dr. Beard's question, yes.—ED.

The Cost of Backache

To THE EDITOR: The recent report by Dr Homer Pheasant [Pheasant HC: Backache—Its nature, incidence and cost. West J Med 126.330-332, Apr 1977] highlights the great social importance of backache and the expense incurred by either medical or surgical treatment. Discomfort and suffering caused by spinal diseases is another important factor which should encourage physicians to seek improved methods of treatment for backache.

Unfortunately, a cursory reading of this article would suggest that medical treatment for spine pathology is preferable to surgical treatment. This is suggested since medical treatment is less expensive. I would certainly agree that in the overwhelming majority of patients with backache surgical treatment is not required However, to indict surgical therapy without consideration of selection of patients for treatment is inappropriate.

Dr. Pheasant states "costs for surgical treatment exceeded medical costs." A more accurate comment might be "costs for treatment of backache which requires surgical therapy exceeds the cost for treatment of backache which does not require surgical therapy." I would have expected an extruded lumbar disc to require more expensive care than a sprain.

C A. COBB, III, MD
Sacramento

Immunization and Health Education

To THE EDITOR: The article by Dr. Billstein on school-based immunization clinics [Billstein S: School-based immunization clinics—A method for raising community immunization levels (Public Health). West J Med 126:73-78, Jan 1977] has a number of erroneous concepts that need comment.

(1) "The cost per child screened was $1.93," "cost per child screened was $2.26." What is this cost in a private setting? $0. This screening is part of routine periodic evaluations and no additional personnel need be salaried.

(2) ". . . no additional direct cost to the parents (because it is funded by tax money)." Who does Dr. Billstein think pays the taxes? Why is this type of program given a financial advantage over the private sector? If tax monies were utilized to supply private doctors with vaccines, they could be administered at reduced cost.

(3) Out of 88,304 immunizations, a total of 16 untoward reactions are noted. I would really question if all were reported. Who was available to answer questions after school hours and on weekends? What telephone numbers were given to parents to report reactions? It is nice that a program like this can function during normal awake hours and then is allowed to fade into oblivion once the sun has set or the five o'clock whistle has blown.

(4) "It also enables schools to update records of the children's immunization status and, it is to be hoped, prevents outbreaks. . . . ." From this statement, one can assume that record keeping is the program's primary function and disease control an incidental spin-off. $147,654.64 for record keeping!

(5) The implied conclusion drawn from the 1975 outbreak, that the early school population was protected by these clinics in contrast to the junior high school group, is totally misleading. All outbreaks in 1975 were highest in the teenage group, whether the immunizations were done in private or public clinics. All groups, private and public, found a low incidence of disease in the early school years, because of a change in their immunization programs due to newfound information concerning rubeola immunizations. The implication of merited credit for medical data that were to be forthcoming and could have been shown by any and all other immunization agencies is—in the common teenage language—"gross."

It is a mutually acceptable concern of all physicians that immunization rates be maximized. Perhaps if those in public health were to concentrate their efforts on health education and the philosophy of having each child identify with his own primary source of care, it would be a better expenditure of tax dollars.

DAVID M. ROSENTHAL, MD
Sunnyvale, California

Dr. Billstein responds

TO THE EDITOR: I am happy to respond to Dr. Rosenthal's questions.

Question 1

If we assume that half to two thirds of children attend a private physician's office for well-child care and, therefore, get their immunizations via that route, then the cost of screening would be incorporated into the fees charged by the pediatricians or family practitioners. Therefore, that total cost is unknown.

Unfortunately, when we screened the schools in Sacramento, a number of children received some of their immunizations via this route and for a variety of reasons[1] never completed the school entrance requirements. Therefore, making sure that the community immunization levels were high enough so that outbreaks of these diseases would not occur was delegated to the Public Health Department.

Question 2

Currently all polio vaccine and measles-rubella vaccine are available free to private physicians via their local public health department providing no charge is levied for the vaccine. This offer was made to the Sacramento Medical Society's physicians and we had only two takers. Federal funds currently support this program.

If Dr. Rosenthal has read about the recent measles epidemic in Los Angeles (San Francisco Chronicle, May 3, 1977, p 3), then he would know that apparently the private medical sector has not been able to keep the total community's immunizations at a protective level wherein epidemics no longer occur. Many reasons for this are postulated.

Question 3

The Sacramento County Health Agency has a physician on call 24 hours a day, seven days a week, to field all medical calls. The county emergency number was made available at the clinics and could and can also be obtained by dialing the local operator.

Question 4

The purpose of the school health record is to comply with the laws requiring immunizations for school admission and also so that school nurses may keep a surveillance on the health of their respective schools and their children.

Question 5

The answer remains the same as cited in the paper, children that were inadequately immunized to rubeola required another immunization. This was not done by the private or public sectors of medicine routinely even though the facts were known since 1967.

I hope these replies answer Dr. Rosenthal's questions.

STEPHEN BILLSTEIN, MD
San Francisco

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Refer to: Rose EK: Bringing costs under control (Special Article). West J Med 126:513-516, Jun 1977

Special Article

Bringing Costs Under Control

E. KASH ROSE, MD, *Napa, California*

EVERY MONTH the American Way is being tested when we sit down and pay our bills. If you were to drop in at this moment of truth around America, you would hear more and more people questioning them, for they reflect the inflation that has made a nightmare of our ability to meet financial obligations.

At the top of many of these piles of bills are medical bills. They, themselves, may not seem to be unduly hard to pay—after all, 90 percent of all Americans are covered to some extent by medical insurance.

On the other hand they often can be very hard to pay. People may have had unusually large medical expenses, but no catastrophic insurance coverage. Even with insurance, they may find the portion that they themselves must pay is larger because the total number of medical bills today is larger. On top of this are the hidden costs—costs in the form of pay that the employee does not take home, income he never sees directly because it is paid to him by his employer in the form of a group medical insurance plan, and the ever-increasing taxes for Medicare and Medi-Cal.

Last year, health care costs totaled $140 billion in the United States. That is 8.6 percent of the gross national product. Less than 20 percent of the money spent for health care goes to physicians, although physicians "control" a significantly larger percentage by calling for hospital admissions, laboratory tests and prescriptions. Medicare and Medicaid are now at the $40 billion mark. That is where the total national health expenditure was in 1965, just before those two programs were created. Between 1950 and 1976, the cost of a day in the hospital climbed five times as fast as the general inflation rate, reaching an average of $175 last year, up from $16 a day in 1950. I have seen some projections of the current trend in health care costs that are astounding. For the year 2000, some projections are for an astronomical $500 billion a year for health care in this country, and some even give figures over a trillion. It does not take much imagination to recognize that this represents a problem for us all.

The way this problem is solved will determine whether patients will receive the same high quality care that they receive today, as well as whether medicine will remain a profession that any one can find satisfying to pursue in the challenging years ahead. The answer to those questions lies, I think, in the answer to a larger question. Do we Americans want more government, more taxes and more regulations? (That is the direction we have been going for some time.) Or are we ready for less government, less bureaucratic interference, and a chance, once again, to be more self-reliant? I am sure physicians would answer that last question with a resounding "Yes!" I am not so sure how patients would answer it. I think that the way out of this potential health-care cost crisis is individual effort.

To help me answer the dilemma posed by the increased cost of health care, I sent a number of letters to specialty societies in California, asking

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These remarks are based on the Inaugural Address of Dr. Rose as President of the California Medical Association, presented March 7, 1977.

Reprint requests to: Division of Professional and Public Relations, California Medical Association, 731 Market Street, San Francisco, CA 94103.

the question "What can we do, not only as an organization, but also as individual physicians and individual members of our specialty societies and hospital medical staffs, to diminish this escalation of medical costs?" Here are a few excerpts from the responses:

Dr. John L. Benton, president of the California Society of Internal Medicine, said: "Perhaps the only way (to solve the problem) is to accept the admittedly awesome prospect of a real free enterprise system, and let it be introduced into health care on a rational, reasonable basis." He suggests doctors and hospitals be obliged to truly compete with each other as a means of reducing prices.

Dr. Paul F. Wehrle, district chairman of the American Academy of Pediatrics, wrote:

> From the pediatric point of view, much of the cost increase appears to be related to technical advances. For example, the mortality rate of newborn infants in our institution is approximately 50 percent of the rates observed only 15 years ago. This improvement is associated with the use of intensive-care nurseries, one-on-one staffing and an amazing array of monitoring equipment. Similar changes have been seen in renal programs, cancer chemotherapy, thoracic surgery and many other areas. Perhaps the only rational approach is to attempt to identify relative contributions to the cost increases so that the public, the insurers and elected representatives can understand the problem more clearly. If the cost required for particular procedures is known and the cost of constructing and equipping hospitals is understood, then society is in a better position to make the necessary decisions and choices.

Dr. Don R. King, president of the California Society of Anesthesiologists, said:

> Patient expectations of superior medical care by specialists has contributed to increased costs. Life expectancy has increased, but there is a dollar cost for the training of all these specialists. An anesthesiologist rather than a nurse administers anesthesia. The family practitioner often quickly refers the severely ill patient to a specialist, and it is not uncommon for a patient to have a cadre of specialty doctors rather than go to a generalist first. It all adds up to increased costs of medical care. Intensive research that led to the polio vaccine, to the development of new antibiotics, to new diagnostic machines have all contributed to longevity.

Dr. J. L. Izenstark, president of the Society of Nuclear Medicine, said: "We need a new educational system to acquaint the public with the fact that not every small ache or small bump requires an X-ray, or, indeed, requires medical attention at all. Although physicians are guilty of overutilization, the biggest overutilizer is the public itself."

Those are some opinions. In my opinion, the key is the individual—the individual physician and the individual patient. A good first step would be for each and every physician to know the exact costs of the specific examinations, services and referrals that he orders for his patients. By knowing these costs, he can be more cautious and more concerned about those costs. He might avoid some tests, for example. Or he might be more hesitant to admit a patient into a hospital when outpatient treatment might be given—which is a lot less expensive than a hospital room at $175 a day. To effect savings, physicians might be less enthusiastic about quickly implementing expensive new technology. They might also coordinate services better, to lessen the duplication of expensive new equipment. The medical profession should question some accepted practices. For example, industry spends millions of dollars on annual physicals, but studies show that those who receive the physicals have the same disease, disability and death rates as people who go to a physician only when they are sick.

Each physician can accept the responsibility for informing his patients about health care costs. In this way the public may better understand the reasons for today's high costs—and may be more motivated to do something constructive about them. Physicians can tell people about professional liability costs, about the costs of defensive medicine and about the costs of new medical technology. They can be told how inflation has undermined the medical dollar, what overutilization of health services does to total costs and what poor health habits are doing to themselves and to their medical bills. The public should be made aware that there is a role for government in health care—but that role is not in taking over the health care system, which would adversely affect patients. Patients should know that more government regulations would mean more medical cost increases to pay for the administration and enforcement of those unneeded and unwanted regulations.

The greatest costs savings, however, would be realized if people accepted the responsibility of regulating their own life-style and their own health care expenditures, instead of having the government do it for them. A study by the United States Department of Agriculture shows that improved nutrition might cut the nation's bill by a third. Physicians have testified before the government that diet may be one of the major causes of Americans' death and disability from coronary artery disease, several of the most important forms of cancer, hypertension, diabetes, obesity and other chronic diseases. Patients should know

this. Carcinoma of the lung has become epidemic, creating vast medical costs. Automobiles are more lethal than wars. More Americans die in automobile accidents every year than were killed in the entire Vietnam War. Or, to give another example, when a motorcyclist is severely injured, because he fails to wear protective clothing, the resulting hospital bills are high. The public should be educated about the cost of reconstructive medicine for such accident victims. People should also be made aware of the enormous drain on the nation's total medical bill because society tolerates poor nutrition and squalid living conditions in ghetto areas throughout America.

The federal Council on Wage and Price Stability's paper entitled "The Rapid Rise of Hospital Costs" concludes that the primary reason for hospital cost inflation is "that patients are now much more willing to pay for expensive care and doctors are much more willing to order it because insurance now finances a much larger share of those payments." The report declares that the increased costs of sophisticated medical equipment and the greater amount of this equipment and the skilled medical employees needed to operate it, are not in themselves the main reason hospital costs have risen sharply. Rather, the paper finds that patients' demands have created the need for more sophisticated medical equipment and for more employees to run it. Our patients should be told of the costs of this demand for more and more medical services, more hospital admissions and more tests. According to the Department of Health, Education, and Welfare the cost of dying is approximately 20 percent of the money spent for health care. This is money spent for tests and hospital stays on patients who have no hope of recovering. It has come time to ask ourselves if we, as a society, prefer to face death in a hospital, or at home.

As to overutilization of medical services, there are several alternative solutions of that problem. First, physical facilities could be limited, meaning fewer hospital beds, fewer new hospitals and less new medical equipment. By limiting what is available, total use inevitably is controlled and sometimes even reduced. Second, the use of medical services could be limited by government regulations. But this means waiting periods for elective surgical procedures and a limit on the number of operations that could be done during any given month. Third, use could be limited by requiring patients to participate in paying the actual cost of their health care. This would mean copayments along with insurance as the rule instead of the exception. If each patient is more responsible for his medical costs, self-limitation is injected into the health cost equation. And there is a fourth alternative: for society to accept the responsibility for complete medical care and unlimited quality medical care for everyone, with the knowledge that this would be very costly no matter what system is devised. Society must then realistically be prepared to pay for this alternative, if it can.

Is the public aware of these alternatives and the relative merits of each—or is it simply waiting for government to offer a seemingly simple solution, perhaps via a federal takeover of the health care system?

Does the public know how much health care will cost if run by the government? Does the public understand that with total government administration of health insurance, it would also get a vast enlargement of the federal bureaucracy, plus billions more in taxes to pay for administration, in contrast to simply spending money for direct patient care? In the long run, society must decide what kind of health care America is going to have in the future. Society must decide whether it wants or can afford the volume and variety of medical wonders now available, or whether it instead is willing to accept modifications in present life-styles and a slowdown in the rate of expansion of medical technology in exchange for more moderate health care costs. There are a lot of hard decisions to make and a lot of hard questions to be answered.

But before society can make these decisions, it must be informed.

I would like to see an effective public information campaign on health care, its costs and the available alternatives. Education is our job and also the govenrment's job. The responsible role of the government is to tell it like it is, instead of accusing hospitals and doctors of charging too much. It should tell the people that the real causes for our health care costs are the environment and our life-styles. This information campaign merits highest priority. We need to tell people how to take better care of themselves. We need to tell people how many expensive hospital beds are being occupied by people because they smoke, drink and maim themselves and each other. We should call for a frontier spirit in a renewed concern by every American for his or her own health.

I would like to see, instead of a federal system of national health insurance, a program of national health information. In my opinion the most significant achievements in health care will be brought about through education, not more and more regulations. It is time for each individual person to show what he can do. It will take individual efforts to stem the rising costs of health care. It will take the individual efforts of patients, and it will take our individual efforts as physicians. If this is done, all of us, working together as concerned individual members of society, can reduce the need for health services and make health care bills in this country easier to pay.

Questions to Ask During Premarital Counseling

Providing premarital counseling is an important step for physicians to be taking. It provides one of the best guarantees for a good, happy marriage and a healthy marriage, because physically healthy and happy families have a close relationship. . . . You can do the usual physical examinations, and have the usual discussions of whatever physiological things you want to discuss, and things of that sort. But also, please, in the midst of this, ask them about possible areas of conflict. . . . Ask them such key questions as: "What time do you get up in the morning . . . and who'll get up first. . . ?" And also, "Who's going to carry out the garbage? . . . If there's going to be some little difference of opinion about it, now's the time to talk about it, before you even get married." . . . Examples of problems of living together—money: "Do you plan to have a joint checking account? What do you think is a good insurance program? Do you believe in credit cards? And which one of you is going to write the checks to pay the bills at the end of the month? . . . Where are you going to spend next Christmas? Vacations? Which one of your in-laws are you going to have the most trouble with? What kind of trouble is that in-law going to cause you? And how are you going to handle it?" Forewarned will make them forearmed, and will save an awful lot of grief.

—BEVERLEY T. MEAD, MD, *Omaha*
Extracted from *Audio-Digest Obstetrics and Gynecology*, Vol. 23, No. 6, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1577 East Chevy Chase Drive, Glendale, CA 91206.

The 85th Annual Meeting

of the

IDAHO MEDICAL ASSOCIATION

JULY 27-30, 1977

at Idaho's SUN VALLEY

An Invitation to SUN VALLEY

JULY 27-30, 1977

I am very pleased to invite you to attend the 85th annual meeting of the Idaho Medical Association at beautiful Sun Valley, July 27 through July 30, 1977.

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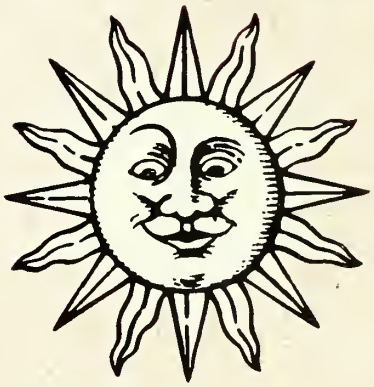
And there is time to enjoy recreational offerings including golf, tennis, swimming, hiking, sightseeing, riding, trapshooting, bowling and more.

We do hope that you will join us.

DONALD R. BJORNSON, MD
President, Idaho Medical Association

85th Annual Meeting
Idaho Medical Association
Sun Valley • July 27-30, 1977



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*European Plan.

IDAHO MEDICAL ASSOCIATION

85th Annual Meeting

Wednesday

8:30 a.m.-5:00 p.m. House of Delegates

Thursday

8:15 a.m. Welcome
DONALD R. BJORNSON, MD, Idaho Falls
President, Idaho Medical Association

Introduction
THOMAS MITCHELL, MD
Program Chairman

8:30 a.m. Dilemmas in Informed Consent
ROGER B. DWORKIN

9:15 a.m. Insomnia
DAVID RASKIN, MD
Associate Professor, Department of Psychiatry, University of Washington, Seattle

10:00 a.m. Pharmacological Basis of Drug Interaction
DONALD B. HUNNINGHAKE, MD
Associate Professor of Medicine and Pharmacology, University of Minnesota, Minneapolis

10:45 a.m. Recess to visit exhibits, Continental Room

11:00 a.m. Drug Combinations in Hypertension, Including Possible Interactions
HOWARD MORRELLI, MD
Professor of Medicine and Pharmacology, University of California, School of Medicine, San Francisco

11:45 a.m. Pharmacology of Crash Cart Medications, Including Drug Interactions
PETER BRYSON, MD
Assistant Professor of Medicine, University of Colorado Medical Center and Director of Rocky Mountain Poison Center

12:30 p.m. Adjourn

Friday

8:15 a.m. Introduction

8:30 a.m. Malpractice: A New Approach
ROBERT S. BRITTAIN, MD
President, Institute for Correct Practice, Colorado

9:15 a.m. Malpractice and Legal Reform
ROBERT D. DWORKIN
Professor of Law, Indiana University School of Law, Bloomington, Indiana

10:00 a.m. Diagnosis and Treatment of Depression
DAVID RASKIN, MD

10:45 a.m. Recess to view exhibits

11:00 a.m. Pharmacology of Crash Cart Medications, Including Drug Interactions (Continued)
PETER BRYSON, MD

11:45 a.m. Problems with Clinically Important Drug Interactions
DONALD B. HUNNINGHAKE, MD

12:30 p.m.-1:30 p.m.
MR. ROBERT DERZON
Administrator
Health Care Financing Administration
Department of Health, Education & Welfare

Saturday

8:00 a.m.-1:30 p.m. Closing Session, House of Delegates

For information, contact:

IDAHO MEDICAL ASSOCIATION
407 West Bannock
Boise, Idaho 83702

Telephone: (208) 344-7888

in memoriam

ADAMS, JOEL E., San Bernardino. Died March 17, 1977 in the Dominican Republic of myocardial infarction, aged 68. Graduate of the University of Illinois College of Medicine, Chicago, 1936. Licensed in California in 1946. Dr. Adams was a member of the San Bernardino County Medical Society.

CURY, DAHAR, JR., Lynwood. Died March 28, 1977 in Lynwood of cancer, 56. Graduate of the University of Virginia School of Medicine, Charlottesville, 1945. Licensed in California in 1954. Dr. Cury was a member of the Los Angeles County Medical Association.

DEEN, RICHARD LAMONT, Covina. Died February 15, 1977 in Los Angeles of cancer of pancreas, aged 45. Graduate of St. Louis University School of Medicine, 1956. Licensed in California in 1959. Dr. Deen was a member of the Los Angeles County Medical Association.

EPSTEEN, ABELSON, San Francisco. Died April 23, 1977, aged 87. Graduate of the University of California Medical School, Berkeley-San Francisco, 1915. Licensed in California in 1915. Dr. Epsteen was a member of the San Francisco Medical Society.

FARRINGTON, CHARLES TEMPLE, San Pedro. Died April 4, 1977, aged 69. Graduate of Washington University School of Medicine, St. Louis, 1935. Licensed in California in 1938. Dr. Farrington was a retired member of the Los Angeles County Medical Association.

FISHER, LLOYD D., Oakland. Died April 28, 1977 in Oakland, aged 73. Graduate of the University of California Medical School, Berkeley-San Francisco, 1938. Licensed in California in 1938. Dr. Fisher was a member of the Alameda-Contra Costa Medical Association.

FLYER, HARRY, Los Angeles. Died September 2, 1976 of cancer, aged 67. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1934. Licensed in California in 1934. Dr. Flyer was a member of the Los Angeles County Medical Association.

GENETTI, EMIL J., Monterey. Died March 30, 1977 in San Francisco, aged 62. Graduate of the University of Michigan Medical School, Ann Arbor, 1940. Licensed in California in 1960. Dr. Genetti was a member of the Monterey County Medical Society.

GLAZER, BENJAMIN, Inglewood. Died March 20, 1977 in Los Angeles of heart disease, aged 64. Graduate of Regia Università degli Studi de Bologna, Facoltà di Medicina e Chirurgia, 1937. Licensed in California in 1953. Dr. Glazer was a member of the Los Angeles County Medical Association.

GRIFFIN, THOMAS F., Los Angeles. Died January 24, 1977 in Palm Springs of heart disease, aged 73. Graduate of the College of Osteopathic Physicians and Surgeons, 1933. Licensed in California in 1933. MD degree from California College of Medicine, 1962. Dr. Griffin was a retired member of the Los Angeles County Medical Association.

GROSSMAN, MARTIN HOWARD, Redondo Beach. Died December 1, 1976 in Palos Verdes of heart disease, aged 43. Graduate of the Chicago Medical School, 1959. Licensed in California in 1964. Dr. Grossman was a member of the Los Angeles County Medical Association.

HERZ, MARIA ALTMANN, Los Angeles. Died March 25, 1977 in Los Angeles of Parkinson's disease, aged 80. Graduate of Medizinische Fakultät der Universität Wien, 1925. Licensed in California in 1952. Dr. Herz was a retired member of the Los Angeles County Medical Association.

HOLMAN, EMILE FREDERIC, San Francisco. Died March 19, 1977 in San Francisco, aged 86. Graduate of Johns Hopkins University School of Medicine, Baltimore, 1918. Licensed in California in 1926. Dr. Holman was a retired member of the San Francisco Medical Society.

HUMPHERYS, VAL G., Sacramento. Died February 14, 1977, aged 43. Graduate of the University of Utah College of Medicine, Salt Lake City, 1962. Licensed in California in 1970. Dr. Humpherys was a member of the Sacramento County Medical Association.

JOHNSTON, J. MONTE, Riverside. Died March 27, 1977 in the Canary Island airplane disaster, aged 54. Graduate of the George Washington University School of Medicine, Washington, DC, 1947. Licensed in California in 1948. Dr. Johnston was a member of the Riverside County Medical Association.

KEY, WILLIAM AMOS, San Mateo. Died May 1, 1977 in Burlingame, aged 82. Graduate of the University of California Medical School, Berkeley-San Francisco, 1922. Licensed in California in 1922. Dr. Key was a retired member of the San Mateo County Medical Society.

KOPMAN, HARRY, Woodland Hills. Died March 4, 1977 in Woodland Hills of heart disease, aged 59. Graduate of the University of California Medical School, Berkeley-San Francisco, 1948. Licensed in California in 1948. Dr. Kopman was a member of the Los Angeles County Medical Association.

LOWMAN, CHARLES LEROY, Los Angeles. Died April 17, 1977 in Los Angeles, aged 97. Graduate of the College of Medicine of the University of Southern California, Los Angeles, 1907. Licensed in California in 1907. Dr. Lowman was a retired member of the Los Angeles County Medical Association.

McCanne, J. Art, Pomona. Died August 25, 1976 in Pomona of multiple myeloma, aged 69. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1949. Licensed in California in 1949. MD degree from California College of Medicine, 1962. Dr. McCanne was a member of the Los Angeles County Medical Association.

McCarthy, Joseph Bernard, Carmel. Died April 13, 1977 in Monterey, aged 83. Graduate of the University of Oregon Medical School, Portland, 1925. Licensed in California in 1931. Dr. McCarthy was a member of the Monterey County Medical Society.

McGrath, John G., Napa. Died March 25, 1977 in Napa of cancer, aged 79. Graduate of Cornell University Medical College, New York, 1926. Licensed in California in 1939. Dr. McGrath was an associate member of the Napa County Medical Society.

O'Neill, Thomas Joseph, Los Angeles. Died October 6, 1976 in Los Angeles of heart disease, aged 72. Graduate of St. Louis University School of Medicine, 1929. Licensed in California in 1929. Dr. O'Neill was a member of the Los Angeles County Medical Association.

Overmiller, Wilbur C., Auburn. Died April 17, 1977 in Auburn of metastatic melanoma, aged 60. Graduate of the University of Nebraska College of Medicine, Lincoln, 1942. Licensed in California in 1946. Dr. Overmiller was a member of the Placer-Nevada County Medical Society.

Pederson, Allen J., Santa Cruz. Died April 10, 1977 in Santa Cruz, aged 71. Graduate of Northwestern University Medical School, Chicago, 1932. Licensed in California in 1932. Dr. Pederson was a member of the Santa Cruz County Medical Society.

Rachmel, William, Lancaster. Died January 25, 1977 in Lancaster of heart disease, aged 75. Graduate of St. Louis University School of Medicine, 1927. Licensed in California in 1928. Dr. Rachmel was a member of the Los Angeles County Medical Association.

Ryan, Russell Colquhorn, San Francisco. Died April 16, 1977 in San Francisco, aged 87. Graduate of the Hahnemann Medical College of the Pacific, San Francisco, 1911. Licensed in California in 1911. Dr. Ryan was a retired member of the San Francisco Medical Society.

Schwartz, Monte, Alhambra. Died February 6, 1977 in Los Angeles of heart disease, aged 56. Graduate of the University of California Medical School, Berkeley-San Francisco, 1943. Licensed in California in 1944. Dr. Schwartz was a member of the Los Angeles County Medical Association.

Sherman, Mandel, Los Angeles. Died February 10, 1977 in Los Angeles of heart disease, aged 80. Graduate of Rush Medical College, Chicago, 1921. Licensed in California in 1950. Dr. Sherman was a member of the Los Angeles County Medical Association.

Spickard, Paul W., Los Angeles. Died January 3, 1977 in Idaho Falls of emphysema, aged 80. Graduate of the University of Oregon Medical School, Portland, 1925. Licensed in California in 1948. Dr. Spickard was a retired member of the Los Angeles County Medical Association.

Stiles, William W., Berkeley. Died March 21, 1977 in Berkeley of cancer, aged 68. Graduate of the University of Rochester School of Medicine and Dentistry, 1939. Licensed in California in 1947. Dr. Stiles was an associate member of the Alameda-Contra Costa Medical Association.

Tesler, Isidore, Encino. Died December 1, 1976 in Los Angeles of myocardial infarction, aged 62. Graduate of Baylor University College of Medicine, Houston, 1938. Licensed in California in 1959. Dr. Tesler was a member of the Los Angeles County Medical Association.

Varon, Solomon Jerome, Woodland Hills. Died November 20, 1976 in Woodland Hills of heart disease, aged 45. Graduate of the University of Michigan Medical School, Ann Arbor, 1958. Licensed in California in 1960. Dr. Varon was a member of the Los Angeles County Medical Association.

Vento, John Place, Los Angeles. Died December 13, 1976 in Palm Springs of heart disease, aged 72. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1933. Licensed in California in 1933. Dr. Vento was a member of the Los Angeles County Medical Association.

Wexler, Manuel R., Los Angeles. Died September 27, 1976 in Los Angeles of cancer, aged 65. Graduate of Rush Medical College, Chicago, 1937. Licensed in California in 1937. Dr. Wexler was a member of the Los Angeles County Medical Association.

Willner, Charles Edgar, Walnut Creek. Died May 2, 1977 in Walnut Creek, aged 53. Graduate of the University of California Medical School, Berkeley-San Francisco, 1946. Licensed in California in 1947. Dr. Willner was a member of the Alameda-Contra Costa Medical Association.

Young, Ralf Irwin, Long Beach. Died April 2, 1977 in Long Beach, aged 50. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1953. Licensed in California in 1954. MD degree from California College of Medicine, 1962. Dr. Young was a member of the Los Angeles County Medical Association.

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AMA Challenges in the Courts

One of the professions's major concerns today is government's mounting pressure for increasing regulation of medicine. In response to these challenges, the AMA has taken a new position of advocacy for physicians and the public which has resulted in the AMA's very first lawsuits against the government.

In March 1975, the AMA took HEW to court over its Utilization Review Regulations which required review of all Medicare and Medicaid hospitalizations within 24 hours. The AMA contended the regulations constituted unlawful interference with the rights of physicians and patients. The AMA won its case and HEW withdrew the regulations.

The AMA also initiated legal action against HEW's Maximum Allowable Cost Rule, charging that the rule, which would govern the prescription of drugs for Medicare and Medicaid patients, intrudes on clinical decisions made by physicians. The case is now pending.

The AMA has also joined with co-plaintiffs, the state of North Carolina, the state of Nebraska and the North Carolina Medical Society, in a suit against the Health Planning Act of 1974 which gives the Secretary of HEW sweeping powers over nearly every aspect of health care.

These are just some of the many actions the AMA has taken to protect your rights and interests and the rights and interests of your patients. With your support, it can be even more effective.

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THIS LISTING of continuing education programs in California and Hawaii is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Committee on Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103; or phone (415) 777-2000, ext. 146. For a list of organizations approved for Category I credit toward the CMA Certificate in Continuing Medical Education or for more information on accreditation or certification, please write to the above address.

CANCER

June 18—**Newer Concepts of Cancer Treatment and Diagnosis for the Practicing Physician.** Presbyterian Intercommunity Hospital and American Cancer Society at Presbyterian Intercommunity Hosp., Whittier. Saturday. 5 hrs. $10. Contact: Elsie Camp, CMA, c/o Glenn Tisman, MD, 2101 W. Beverly Blvd., Montebello 90640.

June 20-24—**Head and Neck Oncology.** UCLA. Monday-Friday.

June 29-July 1—**Newer Concepts of Integrated Cancer Management.** UCSD. Wednesday-Friday.

August 10—**G. I. Carcinoma.** LLU. Wednesday. 4 hrs. $25.

September 12-16—**Medical Oncology Review Course—Third Biennial.** American College of Physicians and Huntington Memorial Hospital, Pasadena. Monday-Friday. Contact: Mrs. Arlene Ellis, Coord., Med. Staff Affairs, Huntington Mem. Hosp., 100 Congress St., Pasadena 91105.

September 17—**Clinical Implications of New Diagnostic Techniques—Ultrasound, Cat Scan, Radioisotopes, Clinical Chemistry.** San Francisco Regional Tumor Foundation at Fireman Fund Building, San Francisco. Saturday. 4 hrs. Contact: Norma Schlager, PhD, S.F. Regional Tumor Foundation, 14th and Lake, San Francisco 94118. (415) 221-2132.

October 3-7—**Medical Oncology Review.** American College of Physicians and Huntington Memorial Hospital at Huntington Sheraton Hotel, Pasadena. Monday-Friday. 36 hrs. $140, ACP members; $200, nonmembers. Contact: Arlene Ellis, Coord., Med. Staff Affairs, Huntington Mem. Hosp., 100 Congress St., Pasadena 91105. (213) 440-5176.

MEDICINE

June 18—**Allergy for the Office Practice.** PMC. Saturday.

June 21-October 25—**Intensive Review of Recent Advances in Internal Medicine—3rd Annual.** UCLA. Tuesday evenings. 60 hrs. $165.

June 24-26—**Dermatomycology.** UCSF. Friday-Sunday. 14 hrs. $250.

July 1-3—**Arthritis Education Workshop.** STAN. Friday-Sunday.

September 7-11—**Medical Knowledge Self-Assessment Program Course.** American College of Physicians at Golden Gateway Holiday Inn, San Francisco. Wednesday-Sunday. 30 hrs. $140, ACP members; $200, nonmembers. Contact: ACP, 4200 Pine St., Philadelphia, PA 19104.

September 9-10—**Skin Flap.** UCSF. Friday-Saturday.

September 14-16—**Pediatric Dermatology.** STAN. Wednesday-Friday. 23 hrs. $225.

September 26-30—**Medical Knowledge Self-Assessment Program Course.** American College of Physicians at Hilton Hotel, Los Angeles. Monday-Friday. 30 hrs. $140, ACP members; $200, nonmembers. Contact: ACP, 4200 Pine St., Philadelphia, PA 19104.

September 29-30—**Annual Physician Postgraduate Symposium on Heart Disease.** San Francisco Heart Assn. and Council on Atherosclerosis, American Heart Assn., at Golden Gateway Holiday Inn, San Francisco. Thursday-Friday. Contact: Molly Austin, Assoc. Dir., S.F. Heart Assn., 421 Powell, San Francisco 94102. (415) 433-2273.

September 29-30—**Clinical Immunology/Rheumatology Update.** UCSF. Thursday-Friday.

October 1-8—**Cardiology.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 29 hrs. $300.

October 3-7—**Medical Oncology Review.** See Cancer, October 3-7.

October 5—**Digitalis: New Insights at the Bicentennial.** L. A. Society of Internal Medicine at L.A. Co. Med. Assn., Los Angeles. Wednesday. 1½ hrs. $7.50 for dinner. Contact: Thomas T. Yoshikawa, MD, LASIM, 5410 Wilshire Blvd., Los Angeles 90036. (213) 937-5514.

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KEY TO ABBREVIATIONS AND SYMBOLS

Medical Centers and CMA Contacts for Information

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103. (415) 777-2000.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Duane Dillman, PhD, Director, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 564-5911, ext. 391.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr., MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, Ext. 2400.

PMC: Pacific Medical Center
Contact: Martin Brotman, MD, Chairman, Education Committee, Pacific Medical Center, P.O. Box 7999, San Francisco 94120. (415) 563-4321, ext. 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Neil C. Andrews, MD, Chairman, Department of Postgraduate Medicine, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, California College of Medicine, Irvine
Contact: Robert Combs, MD, Associate Dean, Continuing Medical Education, University of California, Irvine—California College of Medicine, Irvine 92717 (714) 833-5991.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, P.O. Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: David Allan, MD, Associate Dean for Continuing Medical Education, 1309 Basic Sciences Building, University of California, San Diego, School of Medicine, La Jolla 92037. (714) 452-3708.

UCSF: University of California, San Francisco
Contact: Malcolm S. M. Watts, MD, Associate Dean and Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 226-2047.

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(Continued from Page 22)

October 5-6—**American Heart Association, Greater Los Angeles Alliliate—45th Annual Fall Symposium and 10th Annual Grillith Lecture.** Hilton Hotel, Los Angeles. Wednesday-Thursday. 12 hrs. $65, member of any Heart Assn.; $85, nonmember. Contact: LaVerna Titus, AHA, Greater L.A. Affiliate, 2405 W. 8th St., Los Angeles 90057. (213) 385-4231.

October 6-7—**Pediatric Nephrology.** UCSF. Thursday-Friday.

October 7-8—**Techniques for Dermatologic Research in the Office.** UCSF. Friday-Saturday.

October 8-15—**Endocrinology/Nephrology Review.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 29 hrs. $300.

October 10-13—**Electrocardiography.** PMC at Golden Gateway Holiday Inn, San Francisco. Monday-Thursday.

October 10-14—**Practical Electro-Cardiography.** Memorial Hospital Medical Center of Long Beach-UCI at Hotel Inter-Continental, Maui, Hawaii. Monday-Friday. $150. Contact: Exec. Sec., Center for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

October 21-22—**Diabetes.** STAN and Santa Clara County Diabetes Society. Friday-Saturday.

October 26—**Consultations in Hypertensions.** UCSD at Vacation Village, San Diego. Wednesday.

November 3-6—**California Society of Internal Medicine—Annual Meeting.** Canyon Hotel, Palm Springs. Thursday-Sunday. Contact: CSIM, 703 Market St., Suite 1412, San Francisco 94103. (415) 362-1548.

November 4-5—**Venous Thromboembolism.** PMC at Fairmont Hotel, San Francisco. Friday-Saturday.

November 7-11—**Pediatric Allergy and Clinical Immunology.** UCSF. Monday-Friday.

November 9—**Endocrinology Seminar.** LLU. Wednesday. 4 hrs. $25.

November 26-December 3—**Lymphoproliferative Disorders.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 29 hrs. $300.

December 1-3—**Infectious Disease.** UCSD at Hilton Inn, San Diego. Thursday-Saturday.

December 7—**Lyman A. Brewer III Cardiothoracic Symposium—3rd Annual.** LLU at Hilton Hotel, Los Angeles. Wednesday. 8 hrs. $50.

December 10—**Pulmonary Artery Catheters and Ventilators.** PMC. Saturday. 6 hrs. $300.

OBSTETRICS AND GYNECOLOGY

August 6-8—**Comprehensive Laparoscopy.** UCSD at Sea Lodge, San Diego. Saturday-Monday.

August 27-September 2—**Edward Tyler Symposium on the Practical Management of the Infertile Couple.** Tyler Medical Clinic, Los Angeles, and Univ. of Hawaii School of Medicine at Royal Lahaina Hotel, Maui, Hawaii. One week. 16 hrs. $125. Contact: Exclusive Travel, 3345 Wilshire Blvd., Los Angeles 90010.

October 12-16—**Pacific Coast Fertility Society—Annual Meeting.** Canyon Hotel, Palm Springs. Wednesday-Sunday. 21 hrs. $15, member; $25, nonmember. Contact: Ronald S. Swerdloff, MD, PCFS, 5410 Wilshire Blvd., Los Angeles 90036. (213) 937-5514.

October 14-15—**Office Gynecology Workshop.** PMC. Friday-Saturday.

November 10-12—**Medical Complications of Obstetrics and Gynecology—Annual Fall Seminar in Obstetrics and Gynecology.** UCSF at Mark Hopkins Hotel, San Francisco. Thursday-Saturday.

November 12-14—**Comprehensive Laparoscopy: Current Principles and Practice.** UCSD at Kona Kai Club, Kona, Hawaii. Saturday-Monday.

November 12-19—**Workshops in High Risk Pregnancy: Infertility.** UCSF at Royal Lahania Hotel, Maui, Hawaii. One week.

PEDIATRICS

June 17—**Conference on Prematurity—16th Annual.** STAN. Friday. Contact: Philip Sunshine, MD, Dept. of Pediatrics, Stanford Univ. Sch. of Med., Stanford 94305.

June 22-24—**Pediatric Gastroenterology.** UCSF. Wednesday-Friday.

September 14-16—**Pediatric Dermatology.** See Medicine, September 14-16.

September 15-16—**Pediatric Urology.** See Surgery, September 15-16.

September 28-29—**Brennemann Memorial Lectures—34th Annual.** L.A. Pediatric Society at Bonaventure Hotel, Los Angeles. Wednesday-Thursday. Contact: Eve Black, Exec. Sec., LAPS, P.O. Box 2022, Inglewood 90305. (213) 757-1198.

October 6-7—**Pediatric Nephrology.** See Medicine, October 6-7.

October 15-22—**Pediatrics for the Practitioner.** Children's Hospital of Long Beach and American Academy of Pediatrics, Chapter 2, at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. Contact: Margaret Frederick, Exec. Sec., Center for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

October 21-22—**Adolescent Sexuality and Related Problems.** UCD at Red Lion Motor Inn, Sacramento. Friday-Saturday.

November 4-5—**Children's Experiences of Health and Illness.** UCD at Claremont Hotel, Berkeley. Friday-Saturday.

November 7-11—**Pediatric Allergy and Clinical Immunology.** See Medicine, November 7-11.

December 3—**Practical Aspects of Sports Medicine for Pediatricians.** American Academy of Pediatrics, Calif. Chapter I, Dist. IX, at Union Square Holiday Inn, San Francisco. Saturday. Contact: Martin Gershman, MD, 595 Buckingham Way, San Francisco 94132.

PSYCHIATRY

June 17-19—**Madness and Social Policy.** Mental Research Institute at Cabana Hyatt House, Palo Alto. Friday-Sunday. $75. Contact: Ms. L. Sheffet-Keys, MRI, 555 Middlefield Rd., Palo Alto 94301. (415) 321-3055.

June 27-July 1—**Comparative Psychiatric Therapies: The Difficult to Treat Patient.** USC at Vacation Village, San Diego. Monday-Friday. 21¼ hrs. $200.

September 24-25—**Drug Abuse (Psychopharmacology).** UCLA. Saturday-Sunday. 14 hrs. $140.

October 28-29—**Psychological and Medical Management of Stress.** UCLA at Beverly Hilton Hotel, Beverly Hills. Friday-Saturday. 12 hrs.

November 14-18—**Group Therapy Seminars.** UCSF at Merritt Hotel, Oakland. Monday-Friday.

RADIOLOGY AND PATHOLOGY

June 18-25—**Lab Management for Pathologists.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week.

June 19-24—**Pathology of the Lung.** UCSD. Sunday-Friday.

September 14—**Diagnostic Radiology.** LLU. 4 hrs. $25.

September 17—**Radiology Symposium—5th Annual.** Southern Calif. Permanente Medical Group at Bonaventure Hotel, Los Angeles. Saturday. Contact: Shirley Gach, So. Calif.

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Permanente Med. Grp., Education and Research Dept., 4900 Sunset Blvd., Los Angeles 90027. (213) 667-4241.

September 17—**Clinical Implications of New Diagnostic Techniques—Ultrasound, Cat Scan, Radioisotopes, Clinical Chemistry.** See Cancer, September 17.

October 4-7—**Recent Advances in Diagnostic Radiology.** UCSD. Tuesday-Friday.

October 8-16—**Body Imaging Conference—2nd Annual.** West Park Hospital, Canoga Park, at Kauai Surf Hotel, Kauai, Hawaii. One week. 25 hrs. $295. Contact: Ronald J. Freidman, MD, Dept. of Radiology, West Park Hospital, 22414 Roscoe Blvd., Canoga Park 91304.

October 21-23—**Society of Nuclear Medicine—2nd Annual Western Regional Meeting.** Aladdin Hotel, Las Vegas. Friday-Sunday. Contact: Justine J. Lynch, P.O. Box 40279, San Francisco 94140. (415) 647-0722 or (415) 647-5909.

Postgraduate Videotape Programs in Diagnostic Radiology. Developed by Dept. of Radiology, UCSF. 15 programs in all aspects of diagnostic radiology. Outstanding group of national and international guest lecturers in addition to UC staff present basic approaches to radiographic interpretation and technique as well as new research and clinical advances. Contact: Aveleen Blumenstock, Videotape Coordinator, Dept. of Radiology, UCSF, San Francisco 94143. (415) 666-1988.

SURGERY AND ANESTHESIOLOGY

June 16-17—**The Neck and Upper Extremity in Sports.** USC at Airport Park Hotel, Inglewood. Thursday-Friday. 13 hrs. $105.

June 16-18—**Highlights of Ophthalmology.** PMC. Thursday-Saturday.

June 18-19—**American Association for Study of Headache.** See Of Interest To All, June 18-19.

June 19-July 1—**Temporal Bone Surgical Dissection Course.** Ear Research Institute, Los Angeles. Two weeks. $1,200 for otolaryngologists; $900 for residents. Contact: Malcolm D. Graham, MD, Ear Research Institute, 256 S. Lake St., Los Angeles 90057.

July 2-9—**Manipulation, Mobilization and Related Techniques in Treatment of Musculo-Skeletal and Myofascial Pain Syndromes.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. $275.

July 24-August 5—**Temporal Bone Surgical Dissection Course.** Ear Research Institute, Los Angeles. Two weeks. $1,200 for otolaryngologists; $900 for residents. Contact: Malcolm D. Graham, MD, Ear Research Institute, 256 S. Lake St., Los Angeles 90057.

August 6—**Intensive Care—Fifth Saturday Symposium.** See Of Interest To All, August 6.

August 6-13—**Ophthalmology.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week.

August 13-14—**Clinical Relevance of Recent Advances in Anesthesia: The Critically Ill Child and Adult.** STAN. Saturday-Sunday. 14 hours. Contact: Janie Sydow, Dept. of Anesthesiology, Stanford Univ. School of Medicine, Stanford 94305. (415) 497-6238.

August 15-20—**Intensive Review of Orthopaedic Surgery.** J. Vernon Luck Research Society at Airport Park Hotel, Inglewood. Monday-Saturday. $400. Contact: Chadwick F. Smith, MD, 2400 S. Flower St., Los Angeles 90007.

August 27-September 2—**Edward Tyler Symposium on the Practical Management of the Infertile Couple.** See Obstetrics and Gynecology, August 27-September 2.

September 9-10—**Trauma.** UCSF at Mary's Help Hospital, Daly City. Friday-Saturday.

September 9-10—**Vascular Surgery.** UCSF. Friday-Saturday.

September 15-16—**Pediatric Urology.** UCD at Hyatt Lake Tahoe. Thursday-Friday. 10 hrs. $150.

September 16-17—**Ophthalmology Update III.** PMC at Golden Gateway Holiday Inn, San Francisco. Friday-Saturday. 13 hrs. $225.

September 16-18—**Advances in Obstetrical Anesthesia.** UCSF at Hyatt on Union Square, San Francisco. Friday-Sunday. 12½ hrs.

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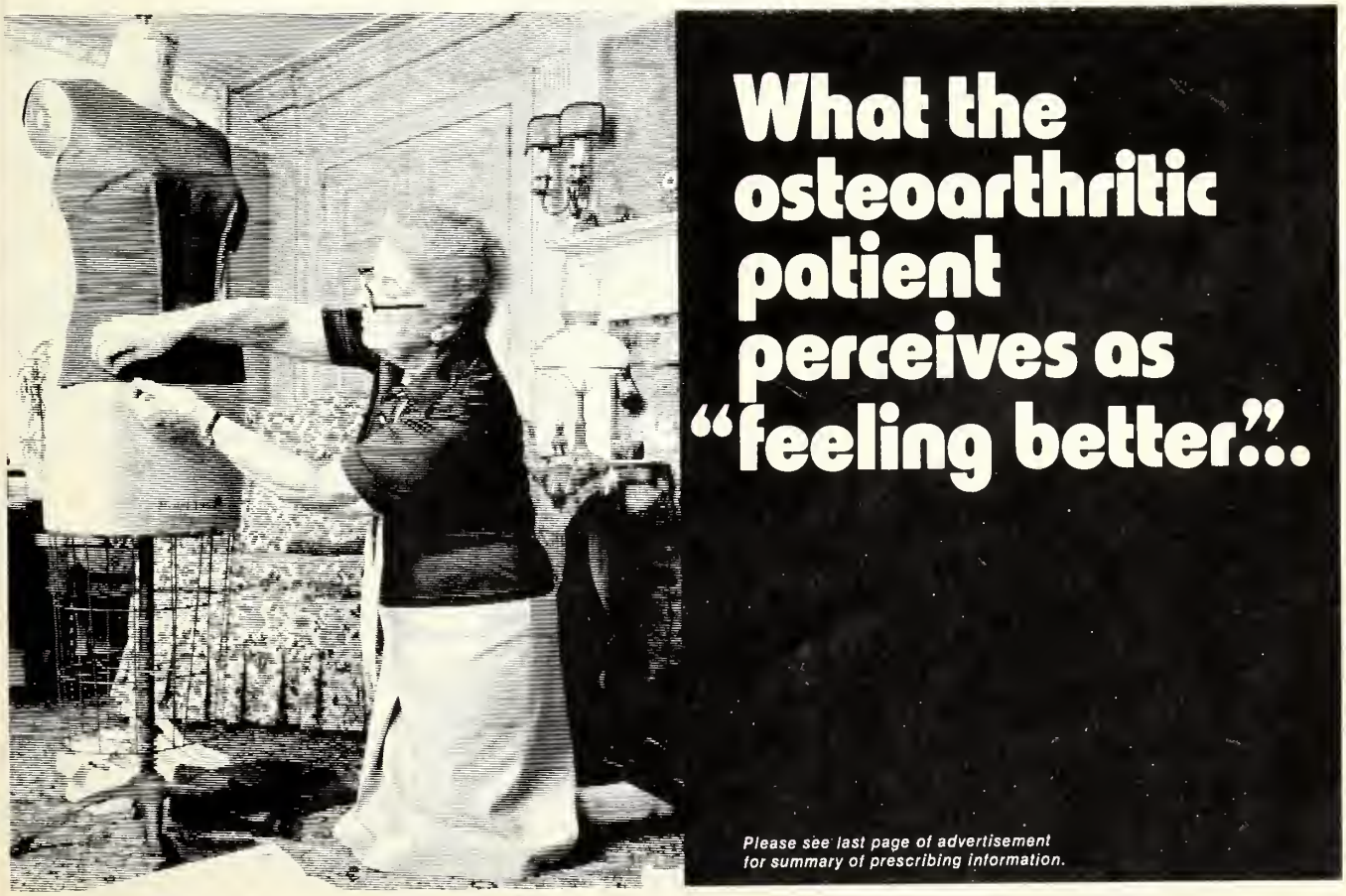

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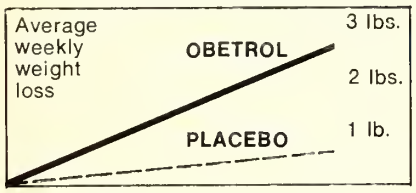

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Actions: Amphetamines are sympathomimetic amines with CNS stimulant activity. Peripheral actions include elevation of systolic and diastolic blood pressures and weak bronchodilator and respiratory stimulant action. The anorectic effect diminishes after a few weeks.

Indications: Exogenous obesity, as a short term (a few weeks) adjunct in a regimen of weight reduction based on caloric restriction. For patients in whom obesity is refractory to other measures.

Contraindications: Advanced arteriosclerosis, symptomatic cardiovascular disease, moderate to severe hypertension, hyperthyroidism, known hypersensitivity or idiosyncracy to the sympathomimetic amines. • Agitated states. • Patients with a history of drug abuse. • During or within 14 days following the administration of monoamine oxidase inhibitors, hypertensive crises may result.

Warnings: Tolerance to the anorectic effect usually develops within a few weeks. When this occurs, the recommended dose should not be exceeded in an attempt to increase the effect, rather, the drug should be discontinued. Amphetamines may impair the ability of the patient to engage in potentially hazardous activities such as operating machinery or driving a motor vehicle; the patient should therefore be cautioned accordingly.

Precautions: Caution is to be exercised in prescribing amphetamines for patients with even mild hypertension. Insulin requirements in diabetes mellitus may be altered in association with the use of amphetamines and the concomitant dietary regimen. Amphetamines may decrease the hypotensive effect of guanethidine. The least amount feasible should be prescribed or dispensed at one time in order to minimize the possibility of overdosage.

Adverse Reactions: *Cardiovascular:* Palpitation, tachycardia, elevation of blood pressure. Central nervous system: Overstimulation, restlessness, dizziness, insomnia, euphoria, dysphoria, tremor, headache; rarely, psychotic episodes at recommended doses. *Gastrointestinal:* Dryness of the mouth, unpleasant taste, diarrhea, other gastrointestinal disturbances. Anorexia and weight loss may occur as undesirable effects when amphetamines are used for other than the anorectic effect. *Allergic:* Urticaria. *Endocrine:* Impotence, changes in libido.

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3. Obesity: Usual adult dose 5 to 30 milligrams per day in divided doses.

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(Continued from Page 25)

October 10-14—**Congress of Neurological Surgeons.** Hilton Hotel, San Francisco. Monday-Friday. 40 hrs. $75, members; $100, nonmembers. Contact: David L. Kelly, Jr., MD, Bowman Gray School of Medicine, Winston-Salem, NC 27103. (919) 727-4653.

October 12-16—**Pacific Coast Fertility Society—Annual Meeting.** See Obstetrics and Gynecology, October 12-16.

October 23-November 4—**Temporal Bone Surgical Dissection Course.** Ear Research Institute, Los Angeles. Two weeks. $1,200 for otolaryngologists; $900, residents. Contact: Malcolm D. Graham, MD, Ear Research Institute, 256 S. Lake St., Los Angeles 90057.

October 28-29—**The Macula.** Retina Research Fund of St. Mary's Hospital and Medical Center at Hyatt on Union Square, San Francisco. Friday-Saturday. Contact: Claire Ohiyon, c/o Howard Schatz, MD, 3637 Sacramento St., San Francisco 94118. (415) 921-4860.

October 30-November 4—**American Society of Plastic and Reconstructive Surgeons—Annual Convention.** Hilton Hotel, San Francisco. Sunday-Friday. 33 hrs. Contact: Linda Campbell, ASPRS, 29 E. Madison St., Chicago 60602. (312) 641-0593.

November 12—**Current Concepts in Ophthalmic Plastic Surgery.** Jules Stein Eye Institute, Los Angeles. Saturday. Contact: Shelley E. Reid, Jules Stein Eye Institute, UCLA Sch. of Med., Ctr. for the Health Sciences, Los Angeles 90024.

November 18-19—**Strabismus.** PMC. Friday-Saturday. 16 hrs.

November 19—**Flexible Bronchoscopy Workshop.** PMC. Saturday. 6 hrs. $300.

November 19-20—**American Society of Anesthesiologists—Regional Refresher Course.** Sahara Hotel, Lake Tahoe. Saturday-Sunday. Contact: ASA, 515 Busse Highway, Park Ridge, IL 60068.

December 2-4—**ENG Workshop.** PMC at Ilikai Hotel, Honolulu. Friday-Saturday. 24 hrs. $395.

December 3—**Emergency Anesthesia.** Sacramento Valley Anesthesia Society; UCD; Calif. Society of Anesthesiologists at Red Lion Motor Inn, Sacramento. Saturday. $50. Contact: John H. Eisele, MD, Dept. of Anesthesiology. UCD Sch. of Med., Davis 95616. (916) 752-2703.

December 7-9—**Annual Ophthalmology Program.** UCSF. Wednesday-Friday.

December 14—**Treatment of Parkinsonism and Modern Concepts.** LLU. Wednesday. 4 hrs. $25.

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OF INTEREST TO ALL PHYSICIANS

June 16-17—**The Neck and Upper Extremity in Sports.** See Surgery, June 16-17

June 18-19—**American Association for Study of Headache—Annual Meeting.** Hyatt on Union Square, San Francisco. Saturday-Sunday. Contact: Seymour Diamond, MD, Exec. Sec., Am. Assn. for Study of Headache, 5252 N. Western Ave., Chicago 60625. (312) 878-5558.

June 18-22—**American Medical Association—126th Annual Convention.** Fairmont Hotel, San Francisco. Saturday-Wednesday. Contact: AMA, 535 N. Dearborn St., Chicago 60610.

June 21-22—**Pain Clinics.** UC-Berkeley Extension and Vallejo General Hospital at University of Calif., Berkeley. Tuesday-Wednesday. $50. Contact: UC Extension, 2223 Fulton St., Berkeley 94720. (415) 642-1064.

June 23-24—**Individual Practice Associations.** American Assn. of Foundations for Medical Care at Holiday Inn, Monterey.

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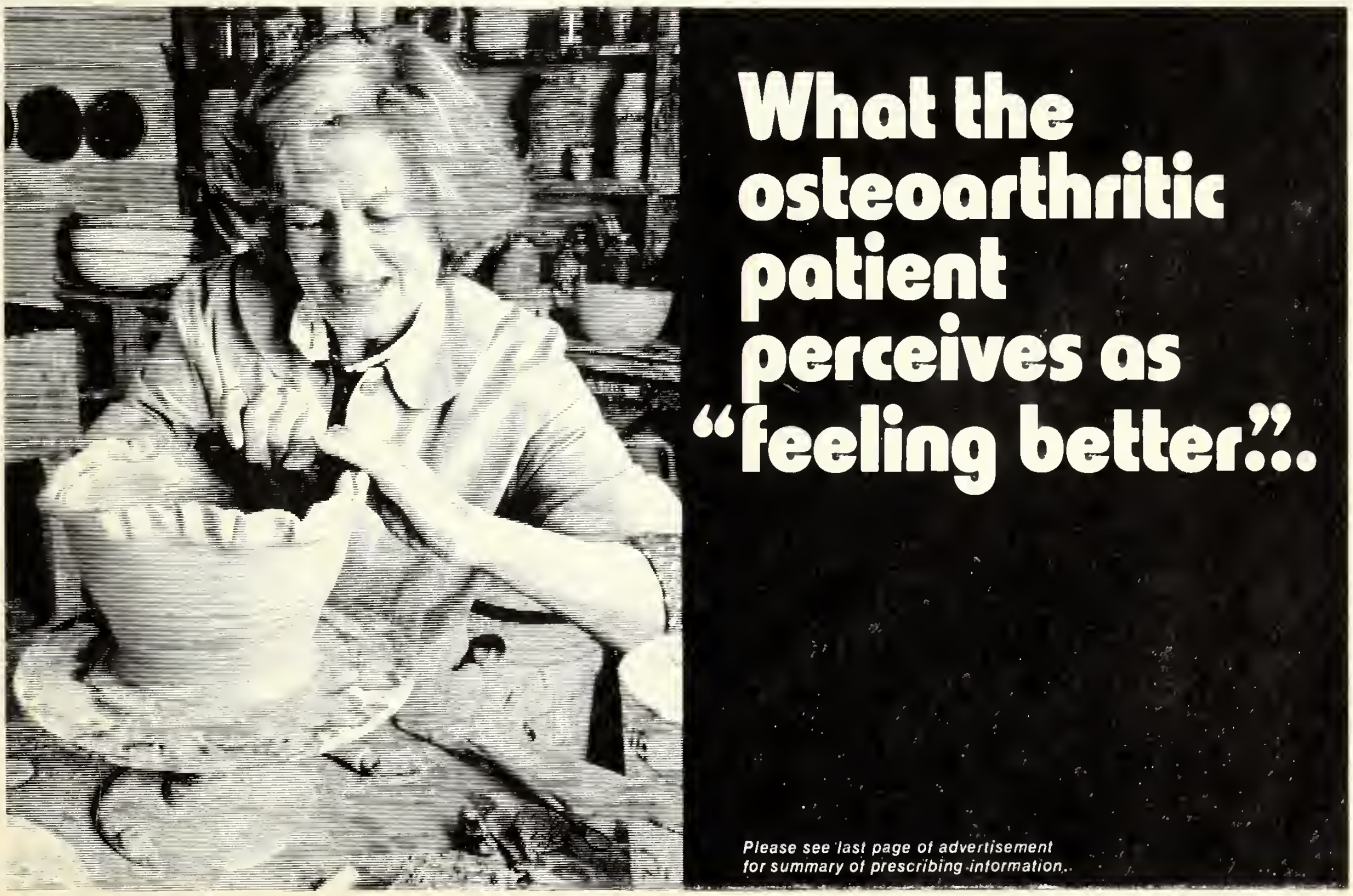

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(Continued from Page 27)

Thursday-Friday. $30, members; $60, nonmembers. Contact: Div. of Cont. Ed., AAFMC, P.O. Box 230, Stockton 95201. (209) 948-4550.

July 8-10, 15-17—**Introduction to Sex Counseling Principles.** UCSF Human Sexuality Program at UCSF. Two weekends. 50 hrs. $175, per person; $300, per couple. Contact: Susan Hansen, Human Sexuality Program, 350 Parnassus Ave., Suite 700, San Francisco 94143. (415) 666-4787.

July 11-15—**Postgraduate Institute for Emergency Physicians, Symposium III.** UCSD at Hilton Hotel, San Diego. Monday-Friday.

July 13—**Problems in Acid Base Balance.** LLU. Wednesday. 4 hrs. $25.

July 25-29—**Family Practice Refresher Course—4th Annual.** UCLA and Santa Monica Hospital at Century Plaza Hotel, Los Angeles. Monday-Friday. 40 hrs. $225.

July 31-August 5—**National Medical Association—82nd Annual Scientific Assembly.** Bonaventure Hotel, Los Angeles. Sunday-Friday. Contact: Alfred F. Fisher, Exec. Dir., NMA, 1625 Eye St., NW, Suite 725A, Washington, D.C. 20006.

August 6—**Intensive Care—Fifth Saturday Symposium.** Mercy Hospital and Medical Center, San Diego. Saturday. 8 hrs. Contact: Gilbert E. Kinyon, MD, Dir. of Anesthesia and Respiratory Therapy, Mercy Hosp. and Med. Ctr., 4077 Fifth Ave., San Diego 92103. (714) 294-8037.

August 8-9—**Autogenic Training and Biofeedback Workshop: Medical Approaches to Homeostatic Self-Regulation.** UCLA at Asilomar, Pacific Grove. Tuesday-Saturday. 24 hrs. $265.

August 13-24—**Postgraduate Refresher Course—20th Annual.** USC at Hawaii. 11 days. 37 hrs.

August 14—**Anatomy.** J Vernon Luck Research Society at Airport Park Hotel, Inglewood. Sunday. $125. Contact: Chadwick F. Smith, MD, 2400 S. Flower St., Los Angeles 90007.

August 15-19—**Postgraduate Institute for Emergency Physicians, Symposium II.** UCSD at Islandia Hotel, San Diego. Sunday-Thursday.

August 22-27—**Family Practice Refresher Course—5th Annual.** UCD at Del Monte Hyatt House, Monterey. Monday-Saturday. 30 hrs. $225.

August 27-September 2—**Edward Tyler Symposium on the Practical Management of the Infertile Couple.** See Obstetrics and Gynecology, August 27-September 2.

August 29-September 3—**Family Practice Refresher Course—8th Annual.** UCI at South Coast Plaza Hotel, Costa Mesa. Monday-Saturday.

August 30-October 18—**Evening Lectures in Medicine.** UCSF at Oakland Hospital, Oakland. Tuesday evenings.

September 19-23—**Topics in Emergency Medicine—Postgraduate Course for Career Emergency Physicians.** UCSF at Ralph K. Davies Medical Center, San Francisco. Monday-Friday. 40 hrs. $300.

September 24-25—**Drug Abuse (Psychopharmacology).** See Psychiatry, September 24-25.

September 25-30—**Postgraduate Institute for Emergency Physicians, Symposium I.** UCSD at Town and Country Hotel, San Diego. Sunday-Friday.

October 1-2—**Nephrology for Family Physicians.** UCLA. Saturday-Sunday.

October 3-7—**Primary Care.** STAN. Monday-Friday.

October 6-8—**Western Occupational Health Conference—21st Annual.** Western Occupational Medical Assn. at Fairmont Hotel, San Francisco. Thursday-Saturday. Contact: B. H. Bravinder, Exec. Sec., WOMA, P.O. Box 201, Alamo 94507. (415) 837-0874.

October 6-9—**Clinical Pharmacology.** UCSF at Hilo, Hawaii. Thursday-Saturday.

October 8—**Selected Topics on Infectious Disease.** PMC. Saturday. 6 hrs.

October 12—**Pain and Its Management.** LLU. Wednesday. 4 hrs. $25.

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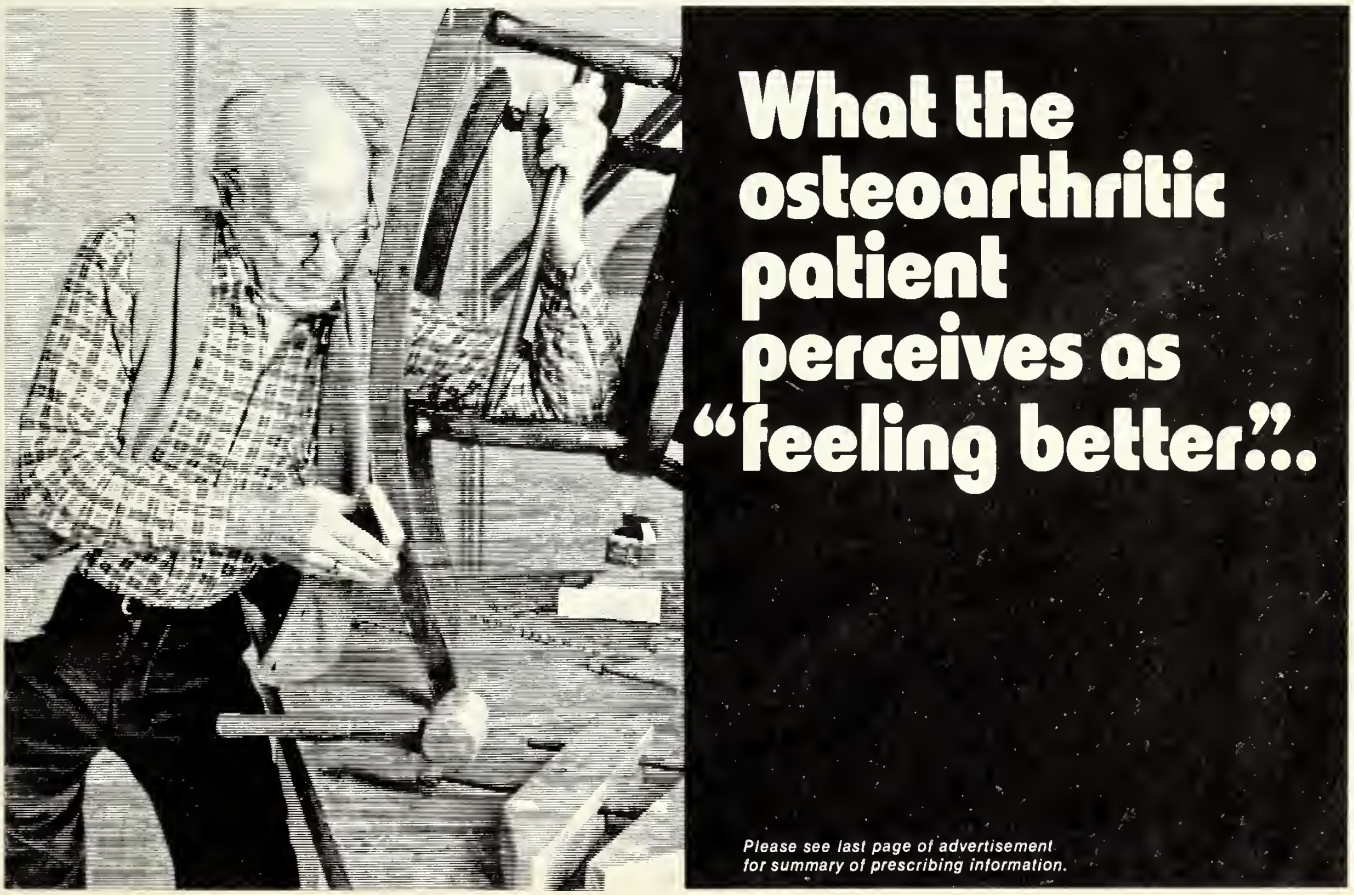

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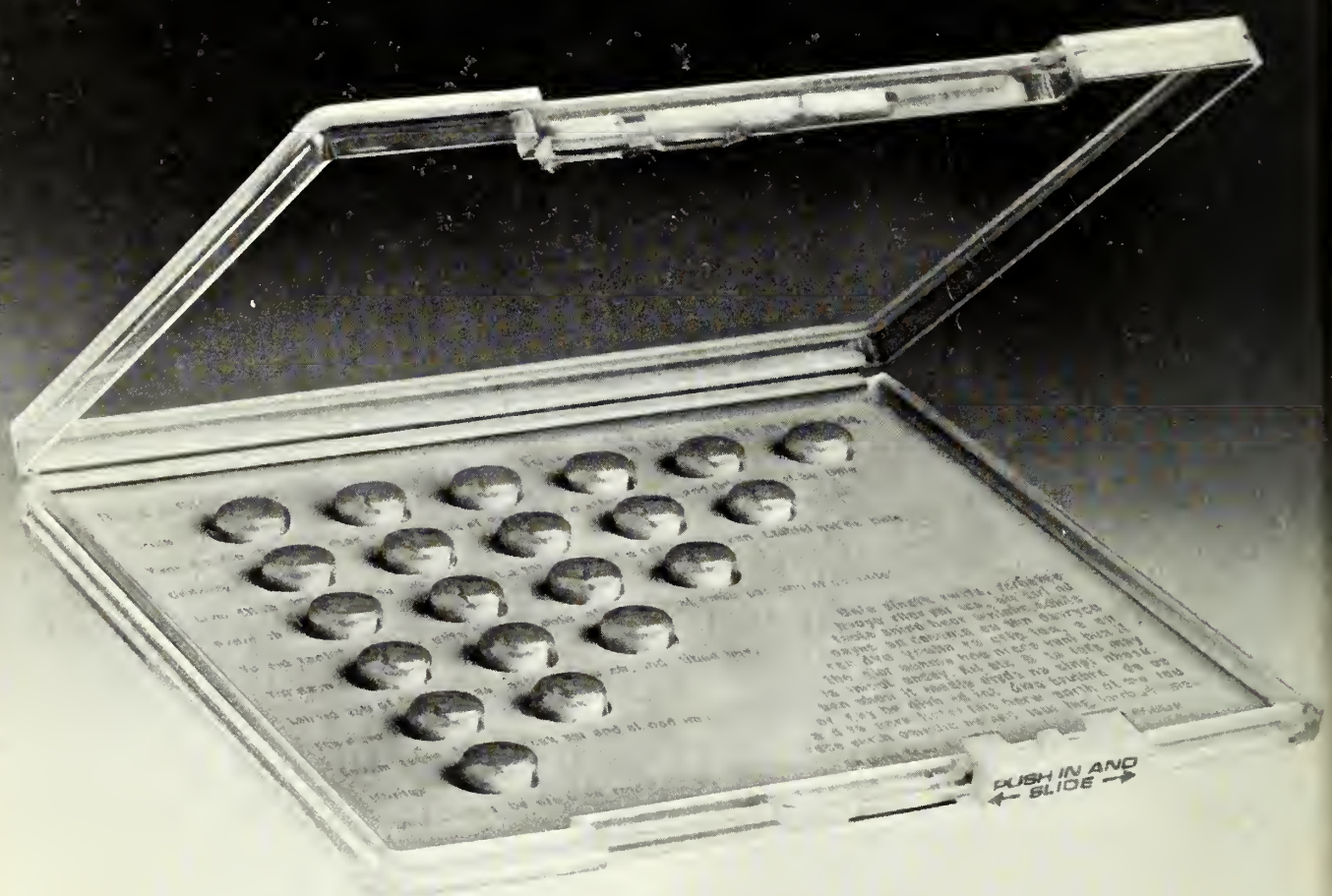

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October 12-14—**Alcoholism Course for Primary Care Physicians.** UCSD at Town and Country Hotel, San Diego. Wednesday-Friday.

October 12-16—**Pacific Coast Fertility Society.** See Obstetrics and Gynecology, October 12-16.

October 14-16, 21-23—**Introduction to Sex Counseling Principles.** UCSF Human Sexuality Program at UCSF. Two weekends. 50 hrs. $175, per person; $300, per couple. Contact: Susan Hansen, Human Sexuality Program, 350 Parnassus, Suite 700, San Francisco 94143. (415) 666-4787.

October 17-21—**Family Practice Review—2nd Annual.** LLU. Monday-Friday. 30 hrs. $150.

October 20-21—**Geriatrics.** UCSF at Veteran's Home of California, Yountville. Thursday-Friday.

October 24-28—**Postgraduate Institute for Emergency Physicians, Symposium III.** UCSD at Vacation Village, San Diego. Monday-Friday.

October 28-29—**Psychological and Medical Management of Stress.** See Psychiatry, October 28-29.

October 30-November 3—**American Medical Association—Regional Meeting.** Sheraton Waikiki, Honolulu, Hawaii. Sunday-Thursday. Contact: AMA, 535 N. Dearborn, Chicago 60610.

October 31-November 4—**Intensive Care.** STAN. Monday-Friday.

November 10-11—**Emergency Medicine (Advanced Course).** UCSF. Thursday-Friday.

November 12-13—**Rheumatology for Family Physicians.** UCLA. Saturday-Sunday.

December 12-16—**Postgraduate Institute for Emergency Physicians, Symposium II.** UCSD at Islandia Hotel, San Diego. Monday-Friday.

December 14—**Treatment of Parkinsonism.** See Surgery, December 14.

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PRECEPTORSHIPS AND TRAINEESHIPS

Training for Physicians in General Internal Medicine. LLU. Four weeks or more, by arrangement. Bedside and classroom training, practical aspects of clinical care and management. 160 hrs. Contact: John E. Peterson, MD, LLU.

Training of Physicians in Modern Concepts of Pulmonary Care. LLU. Four weeks or more, by arrangement. Diagnostic and therapeutic methods in medical chest disease, physiological methodology of modern pulmonary care programs, use of new instrumentation in the field. 160 hrs. Contact: John E. Hodgkin, MD, Chief, Section of Medical Chest Diseases, LLU.

Physician-in-Residence Preceptorship in Pulmonary Disease. USC, Pulmonary Disease Section, Dept. of Medicine and Postgraduate Medical Education. One month or more, by arrangement. Opportunity for practicing physician to achieve specified knowledge and skills in adult pulmonary medicine. Contact: Oscar J. Balchum, MD, PhD, USC.

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effectiveness

The relief of pain and stiffness in patients with osteoarthritis

The improvement in mobility in patients with osteoarthritis

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700452
Nalfon®
fenoprofen calcium

Please see last page of advertisement for summary of prescribing information

TWENTY-FIRST ANNUAL
WESTERN OCCUPATIONAL HEALTH CONFERENCE
Fairmont Hotel—San Francisco

"Carcinogens, Mutagens and Teratogens: Some Delayed Effects of the Occupational Environment"

THURSDAY, OCTOBER 6

CONCURRENT SESSIONS
Open to All Conference Participants

American Industrial Hygiene Association
Western Occupational Medical Association
American Society of Safety Engineers
Health Physics Society
Western Association of Occupational Health Nurses

FRIDAY, OCTOBER 7

WELCOME
WILLIAM WHITING, MD, FAOMA
California State Compensation Insurance Fund
Chairman, Western Occupational Health Conference

KEYNOTE ADDRESS—"Occupational Health as a Team Effort: The Challenge of Environmental Carcinogens"
EULA BINGHAM, PhD, Assistant Secretary of Labor for Occupational Safety and Health (OSHA)

"Legislative Responsibility"
SPEAKER—ARLEN GREGORIO
California State Senate, Tenth District
Chairman of the State Senate Health and Welfare Committee

PANEL AND OPEN FORUM
"New Developments"
JEAN S. FELTON, MD, FAOMA, Moderator
Long Beach Naval Shipyard
"Scientific Judgment and Zero Concept"
HAROLD HODGE, PhD, University of California, San Francisco
"The Recognition of Mutagens"
BRUCE AMES, PhD, University of California, Berkeley
"Variability of Host Response"
NICHOLAS PETRAKIS, MD, University of California, San Francisco

PANEL AND OPEN FORUM
"Prevention and Control"
REYNOLD T. SCHMIDT, MD, FAOMA, Moderator
Union Oil Company
"The Viewpoint of the Physician"
DAVID P. DISCHER, MD, FAOMA, Stanford Research Institute
"The Viewpoint of the Environmental Toxicologist"
NICK PROCTOR, PhD, Kaiser Aluminum & Chemical Corporation
"The Viewpoint of the Health Physicist"
AMELIA A. HAGAN, MS, Energy Research and Development Administration (ERDA)

SATURDAY, OCTOBER 8

"The Unborn Child and the Workplace"
MODERATOR—PIERO MUSTACCHI, MD, FACP
University of California, San Francisco

"Teratogenesis: Its Impact on the Fertile Working Woman"
SPEAKER—ANN WOLVER, Syntex Corporation

PANEL AND OPEN FORUM
"Fair Employment Practice Commission (FEPC)"
KATHRYN E. RINGGOLD, Attorney-at-Law
"The Law and Employment Practices"
LEONORA M. STOPOL, Acting General Counsel
Fair Employment Practice Commission (FEPC)

CONTINUING EDUCATION CREDENTIALS
AMA Credit, Category I CMA credit. Continuing education credits for State of California registered nurses will be available.

AIHA CERTIFICATION EXAMINATION
The AIHA will hold both the core and comprehensive certification examinations for industrial hygienists on October 4 and 5, 1977. Applications can be made through the AIHA.

EXHIBITORS MAY CONTACT:
Mr. Robert C. Dietrich, Foremost McKesson, Incorporated
Crocker Plaza, 1 Post St., San Francisco, CA 94104

REGISTRATION INFORMATION
Conference and hotel registrations will be mailed August, 1977. Advance Registration, $20; Fee at Conference, $25; Student Fee, $10

To receive our registration packet and program information, please contact: Mr. B. H. Bravinder, Post Office Box 201, Alamo, CA 94507 (415) 837-0874

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Training for Physicians in Nephrology. LLU. Four weeks or more, by arrangement. Hemodialysis, peritoneal dialysis, renal biopsy, and kidney transplantation. 160 hrs. Contact: Robert E. Soderblom, MD, LLU.

Preceptorships in Cardiology. PMC. By arrangement. $200 per mo.; $500 for 3 mos. Contact: Arthur Selzer, MD, PMC.

Preceptorships in Practical Office Dermatology. PMC. Wednesdays or Fridays, 9:00 a.m.-12:00 noon, for 10 weeks. Periods begin Oct., Jan., or April. $100. Contact: Harold M. Schneidman, MD, Dept. of Dermatology, PMC.

Preceptorships in Infectious Disease. PMC. Full time for four weeks. To be arranged. $250. Contact: Rodney J. Valentine, MD, Chief, Div. of Infectious Diseases, PMC.

Preceptorships in Basic Sciences, Biochemistry and Biophysics, Dermatology, Echocardiography, International Health, Microbiology, Neurological Surgery, Obstetrics and Gynecology, Pediatrics, Pharmacology and Experimental Therapeutics, Physiology, Psychiatry, Urology. UCSF. By special arrangement.

Traineeships in Renal Dialysis. UCSF. By special arrangement.

OREGON

COUNCIL ON MEDICAL EDUCATION

THIS BULLETIN of information regarding continuing education programs and meetings of various medical organizations in Oregon is supplied by the Council on Medical Education of the Oregon Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Council on Medical Education, Oregon Medical Association, 5210 SW Corbett Ave., Portland, OR 97201; or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

University of Oregon Medical School, Department of Internal Medicine, 3181 SW Sam Jackson Park Road, Portland 97201:

Every Tuesday, 8:00 a.m. to 9:00 a.m.—**Internal Medicine Grand Rounds.** Library Auditorium, University of Oregon Health Sciences Center, Portland. Contact: Stephen R. Jones, MD, Department of Internal Medicine, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland, 97201.

Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland 97210:

Every Wednesday, 8:00 a.m. to 9:00 a.m. **Medicine Grand Rounds.** Contact: Chris Cobb, Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland 97210.

University of Oregon Medical School, Infectious Disease Conferences, 3181 SW Sam Jackson Park Road, Portland.

Every Thursday, 12:00 Noon—**Infectious Disease Conference** (through June 2), Room 8B-60 UHS (University Hospital South).

FAMILY PRACTICE

Every Wednesday, 11:00 a.m. to 12:00 Noon. **Family Practice Grand Rounds.** Family Practice Center, University of Oregon Health Sciences Center. Contact: William A. Fisher, MD, University of Oregon Health Sciences Center, Department of Family Practice, 3181 SW Sam Jackson Park Road, Portland 97201.

INTERNAL MEDICINE

Every Tuesday, 8:00 a.m. to 9:00 a.m.—**Internal Medicine Grand Rounds.** Library Auditorium, University of Oregon Health Sciences Center, Portland. Contact: Stephen Jones, MD, Department of Internal Medicine, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland 97201.

OF INTEREST TO ALL PHYSICIANS

June 24—**Fourth Annual Symposium, Infection in Medical Practice.** Jantzen Beach Thunderbird, Portland. Contact:

Ronald N. Jones, MD, Kaiser Foundation Laboratory, 10200 SE Sunnyside Road, Clackamas, Oregon 97015.

July 13-15—**Woodland Park Hospital Summer Symposium on Infectious Diseases.** Thunderbird Motor Inn, Astoria. Contact: R. T. Gustafson, MD, Woodland Park Hospital, 11030 SE Holgate St., Portland 97266.

August 19-20—**Tomlin Memorial Cancer Lectures.** Rogue Valley Country Club, Medford. Contact: Earl L. Lawson, MD, The Medford Radiological Group, PO Box 1747, Medford 97501.

WASHINGTON, ALASKA, MONTANA AND IDAHO

In order to have future activities listed here or to receive information on these and other activities, please write Ms. Joan M. Kelday, Information Specialist, Continuing Medical Education, WAMI Program, University of Washington School of Medicine, Health Sciences Building, SC-64, Seattle, Washington 98195. Phone: (206) 543-6995.

June 17-18—**Mountaineering Medicine.** Friday-Saturday. Virginia Mason Medical Center Auditorium, Seattle. Hours and fee to be determined. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) 223-6898.

June 23-25—**Montana Academy of Family Physicians Annual Meeting.** Thursday-Saturday. Fairmont Hot Springs, Mont. Contact: R. D. Buchanan, MD, PO Box 220, Columbia Falls, MT 59912. (406) 892-3952.

August 29-September 2—**American College of Physicians MKSAP Course.** Monday-Friday. Health Sciences Auditorium, Univ. of Wash., Seattle. 36 hrs. Members, $140; ACP Associates, $70; non-member physicians, $200; residents, research fellows, $140. Contact: American College of Physicians, 4200 Pine St., Philadelphia, PA 19104. (215) 243-1200 or Division of Cont. Med. Ed., SC-64, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-9495.

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For your patients with osteoarthritis, the recommended initial dosage* is

1 Pulvule® q.i.d.

*The dosage may be adjusted in accordance with the patient's condition and changes in disease activity.

The most common type of adverse reaction reported concerned the gastrointestinal system. Dyspepsia occurred most frequently; it was observed in about one of seven patients.

DISTA 700452

Nalfon®
fenoprofen calcium

Please see last page of advertisement for summary of prescribing information

Nalfon®
fenoprofen calcium

Indications and Usage: Nalfon is indicated for relief of the signs and symptoms of rheumatoid arthritis and osteoarthritis. It is indicated in the treatment of acute flares and exacerbations and in the long-term management of these diseases. The safety and effectiveness of Nalfon have not been established in those rheumatoid arthritis patients who are designated by the American Rheumatism Association as Functional Class IV (largely or wholly incapacitated with patient bedridden or confined to wheelchair, permitting little or no self-care).

Contraindications: Nalfon is contraindicated in patients who have shown hypersensitivity to it.

Because the potential exists for cross-sensitivity to aspirin and other nonsteroidal, anti-inflammatory drugs, Nalfon should not be given to patients in whom aspirin and other nonsteroidal, anti-inflammatory drugs induce the symptoms of asthma, rhinitis, or urticaria.

Warnings: Nalfon should be given under close supervision to patients with a history of upper-gastrointestinal-tract disease and only after the Adverse Reactions section has been consulted. Gastrointestinal bleeding, sometimes severe, has been reported in patients receiving Nalfon.

In patients with active rheumatoid arthritis or osteoarthritis who also have an active peptic ulcer, attempts should be made to treat the arthritis with nonulcerogenic drugs. If Nalfon must be given, the patient should be under close supervision for signs of ulcer perforation or severe gastrointestinal bleeding.

In subacute and chronic studies in rats, Nalfon caused interstitial nephritis, glomerulonephritis, and renal papillary necrosis. These abnormalities were dose related and began to appear at doses approximating the human dose. In chronic studies in monkeys, interstitial nephritis also occurred following administration of Nalfon. Although this was seen at doses considerably above the human dose, lower doses were not studied in this species. During the course of the clinical trials, one patient developed bilateral suppurative pyelonephritis, underwent laparotomy, went on to renal failure, and died with a diagnosis of septicemia and renal papillary necrosis. It is not known whether these events were drug related. A few patients developed mild elevations of the BUN during therapy with Nalfon. Since Nalfon is eliminated primarily by the kidney, the drug should not be administered to patients with significantly impaired renal function. It is desirable to perform periodic renal function tests in all patients receiving Nalfon.

Precautions: In chronic studies in rats, high doses of Nalfon caused elevation of serum transaminase and hepatocellular hypertrophy. In clinical trials, some patients developed elevation of serum transaminase, LDH, and alkaline phosphatase which persisted for some months and usually, but not always, declined despite continuation of the drug. The significance of this is unknown. It is recommended that periodic liver function tests be performed in patients receiving Nalfon and that the drug be discontinued if abnormalities occur.

The safety of this drug in pregnancy and lactation has not been established, and its use during these events is, therefore, not recommended. Reproduction studies have been performed in rats and rabbits. When fenoprofen was given to rats during pregnancy and continued to the time of labor, parturition was prolonged. Similar results have been found with other nonsteroidal, anti-inflammatory drugs which inhibit prostaglandin synthetase.

In-vitro studies have shown that fenoprofen, because of its affinity for albumin, may displace from their binding sites other drugs which are also albumin bound, and this may lead to drug interaction. Theoretically, fenoprofen, as well as other nonsteroidal, anti-inflammatory agents, could likewise be displaced. Patients receiving hydantoin, sulfonamides, or sulfonylureas should be observed for signs of toxicity to these drugs. In patients receiving coumarin-type anticoagulants, the addition of Nalfon to therapy could prolong the prothrombin time. Patients receiving both drugs should be under careful observation.

In patients receiving Nalfon® (fenoprofen calcium, Dista) and steroid concomitantly, any reduction of steroid dose should be gradual to avoid the possible complications of sudden steroid withdrawal.

Patients with initial low hemoglobin values who are receiving long-term therapy with Nalfon should have a hemoglobin determination at reasonable intervals.

Peripheral edema has been observed in some patients taking Nalfon, therefore, Nalfon should be used with caution in patients with compromised cardiac function.

Studies to date have not shown changes in the eye attributed to administration of Nalfon. However, because of adverse eye findings in animal studies with some other nonsteroidal, anti-inflammatory drugs, it is recommended that ophthalmologic studies be carried out within a reasonable period of time after chronic therapy with Nalfon has been started and at periodic intervals thereafter.

Since food decreases the blood levels of Nalfon, the drug should be given thirty minutes before or two hours after meals during the daytime.

When phenobarbital, which may enhance the metabolism of Nalfon, is added or withdrawn, dosage adjustment of Nalfon may be required.

Caution should be exercised by patients whose activities require alertness if they experience central-nervous-system side-effects from Nalfon.

Since the safety of Nalfon in patients with impaired hearing has not been established, these patients should have periodic tests of auditory function during chronic therapy with Nalfon.

Nalfon decreases platelet aggregation and may prolong bleeding time. Patients who may be adversely affected by prolongation of the bleeding time should be carefully observed when Nalfon is administered.

Adverse Reactions: *Digestive System*—The most common type of adverse reaction concerned the gastrointestinal system. Dyspepsia occurred most frequently, being observed in about one out of seven patients. Other adverse reactions, in descending order of frequency, were constipation, nausea, vomiting, abdominal pain, anorexia, occult blood in the stool, diarrhea, flatulence and dry mouth.

Three instances of peptic ulceration and/or gastrointestinal hemorrhage that may have been due to the drug and four instances in which drug relationship was questionable were observed in 3,391 individuals to whom the drug was administered for periods of time ranging up to 165 weeks.

In less than 2 percent of patients, the drug was discontinued because of adverse gastrointestinal reactions.

Skin and Appendages—The most common adverse effect was pruritus, which was seen in about one out of ten patients. Other adverse reactions were rash, increased sweating, and urticaria.

In about 1 percent of patients, Nalfon was discontinued because of an adverse effect related to the skin.

Nervous System—The most frequent adverse reaction observed was somnolence, which occurred in about one out of seven patients. Other adverse effects, which occurred less frequently, were dizziness, tremor, confusion, and insomnia.

Nalfon was discontinued in less than 0.2 percent of patients because of these side-effects.

Special Senses—The most common adverse reaction was tinnitus, which was seen in about one out of ten patients. Other reactions observed, in descending order of frequency, were blurred vision and decreased hearing.

In about 0.2 percent of patients, Nalfon was discontinued owing to adverse effects related to the special senses.

Cardiovascular—The most frequent adverse effect observed was palpitations. This was noted in about one out of twenty-five patients. Tachycardia was observed less frequently.

In less than 0.5 percent of patients, Nalfon was discontinued as a result of cardiovascular adverse reactions.

Laboratory—Anemia was noted in about one out of 500 patients. Therapy with Nalfon had to be discontinued in one patient because of anemia. Increase in alkaline phosphatase, LDH, and SGOT was observed (see Precautions).

Miscellaneous—Headache was seen in about one out of seven patients. Less frequently observed, in descending order of frequency, were nervousness, asthenia, dyspnea, peripheral edema, fatigue, malaise, and dysuria. [031677]

Additional information available to the profession on request

DISTA

Dista Products Company
Division of Eli Lilly and Company
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